A Comparative study of Efficacy and Safety of Lornoxicam and Diclofenac as Postoperative Analgesics after Mastoidectomy Surgery

Dissertation submitted to

The Tamilnadu Dr.M.G.R. Medical University

in partial fulfillment for the award of the degree of

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

DEPARTMENT OF PHARMACOLOGY

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI – 11

APRIL 2016

CERTIFICATE

This is to certify that dissertation entitled **"A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF LORNOXICAM AND DICLOFENAC AS POSTOPERATIVE ANALGESICS AFTER MASTOIDECTOMY SURGERY"** presented herein by **DR.R.NALINI** is an original work done by her in the Department of Pharmacology, Tirunelveli Medical College, Tirunelveli for the award of the degree of Doctor of Medicine in Pharmacology during the academic period of 2013-2016.

Dean

Tirunelveli Medical College,

Tirunelveli – 627011

Professor & HOD

Department of Pharmacology

Tirunelveli Medical College

Tirunelveli – 627011

DECLARATION

I solemnly declare that the dissertation titled **"A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF LORNOXICAM AND DICLOFENAC AS POSTOPERATIVE ANALGESICS AFTER MASTOIDECTOMY SURGERY"** is done by me in the department of pharmacology, Tirunelveli Medical College, Tirunelveli.

The dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology.

Place: Tirunelveli

Date:

DR.R.NALINI,

Postgraduate Student,

M.D.Pharmacology,

Department of pharmacology,

Tirunelveli Medical College,

Tirunelveli.

ACKNOWLEDGEMENT

I am grateful to the **Dean, Dr.Sithy Athiya Munavarah MD.,** Tirunelveli Medical College & Hospital, Tirunelveli and the **Vice Principal, Dr. M.S.Kannan MD.,** Tirunelveli Medical College & Hospital, Tirunelveli for permitting me to undertake the study.

I express my profound sense of gratitude to Dr. **J.Ezhil Ramya M.D**., Head of the Department, Tirunelveli medical college, Tirunelveli and my guide for her valuable guidance, inspiration and support during the study period.

I am thankful to **Dr.B.Meenakshi M.D**., Associate professor, who has been the vital source of encouragement throughout the study. I would like to express my sincere thanks to all my Assistant Professors **Dr. A. Dulcie Celia M.D., Dr.A.Geetharani M.D., Dr. Vijay sundar M.D., Dr.Shanthini M.D.,** for their valuable suggestions, guidance and support throughout the study.

I sincerely thank **Dr. Suresh Kumar M.S.,** Professor and HOD, **Dr. Ravikumar M.S.,** Professor and other faculty of the department of otorhinolaryngology for their kind help and valuable advice that helped me to a great extent in completing my dissertation successfully.

I am also grateful to all my postgraduate colleagues for their valuable support rendered during the work. I extend my thanks to all staff members, Department of Pharmacology for their timely help.

I sincerely thank **Mr. A. Heber M.Pharm, (Ph.D)** for expert guidance in statistics. I extend my thanks to all patients for their participation and kind co-operation throughout the study period.

I also express my sincere thanks to my family members for their encouragement and moral support during my study period as a postgraduate.

TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572733-EXT; 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 523/PHARM/2014/30

PROTOCOL TITLE: A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF LORNOXICAM AND DICLOFINAC AS POST OPERATIVE ANALGESICS AFTER MASTOIDECTOMY SURGERY.

NAME OF PRINCIPAL INVESTIGATOR: Dr. R.Nalini, MBBS., DLO.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate in MD Pharmacology
DEPARTMENT & INSTITUTION: Department of Pharmacology, Tirunelveli Medical College

Dear Dr. R.Nalini, *The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 14.05.14.*

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of the Principal Investigator ☐
8. Insurance /Compensation Policy ☐
9. Investigator's Agreement with Sponsor ☐
10. Investigator's Undertaking ☐
11. DCGI/DGFT approval ☐
12. Clinical Trial Agreement (CTA) ☐
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) ☐
14. Clinical Trials Registry-India (CTRI) Registration ☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
    a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
    b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
    c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
    d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
    e. Approval for amendment changes must be obtained prior to implementation of changes.
    f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
    g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

14/5/14

Dr.K.Shantaraman MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

TIRUNELVELI MEDICAL COLLEGE TAMILNADU INDIA

Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

18 A Comparative study of Efficacy and Safety of Lornoxicam and Diclofenac as Postoperative Analgesics after Mastoidectomy Surgery.

39 *Dissertation submitted to*

The Tamilnadu Dr.M.G.R. Medical University

in partial fulfillment for the award of the degree of

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

CONTENTS

A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF LORNOXICAM AND DICLOFENAC AS POSTOPERATIVE ANALGESICS AFTER MASTOIDECTOMY SURGERY

ABSTRACT

INTRODUCTION - Postoperative pain sensation is due to the surgical trauma that occurs during manipulation of tissues. Lornoxicam is a nonselective NSAID and it belongs to oxicams with analgesic and anti-inflammatory properties and it has rapid onset of action when compared to other oxicams and has short halflife. Diclofenac sodium is a cyclooxygenase inhibitor and has been used in the management of postoperative pain for many years. It accumulates in the inflamed tissue and the concentration are maintained higher in plasma for many hours and its active metabolite acts as an analgesic. Aim of the present study is to evaluate the efficacy and safety of the analgesic, Lornoxicam when compared to Diclofenac in the management of postoperative pain following mastoidectomy surgery. **MATERIALS AND METHODS –** In this prospective single blinded study, 80 patients underwent mastoidectomy surgery and they were randomized in to two parallel groups. Group A received injection lornoxicam 8mg and group B received injection diclofenac 75mg given intramuscularly twice daily for the 3 consecutive days. The primary parameter was to analyse the pastoperative pain using Visual analogue scale and Wong Bakers scale. The rescue medication used was injection paracetamol 300mg intramuscular. The secondary parameters are the usage of rescue medication and time to use rescue medication by the patients in each study group. Adverse events reported by the subject or noted by the clinician during the each follow-

up visit were recorded.**RESULTS** – The primary efficacy parameter showed significant reduction in the postoperative pain in the lornoxicam group than the diclofenac group (p value <0.05) throughout the study. 3 (7.5%) patients required rescue medication in lornoxicam group and 11 (27.5%) patients required rescue medication in diclofenac group. Significantly more patients required rescue medication in diclofenac group than the lornoxicam group. The mean time required to use rescue medication in lornoxicam group was 7.33±2.21 hours and for diclofenac group it was 7.09 ± 3.36. Renal and liver function parameters did not show any significant difference between preoperative and postoperative values. No serious adverse event was noted in two groups.**CONCLUSION** - Based on the results of our study we conclude that injection lornoxicam 8mg given intramuscularly is a better analgesic when compared to injection diclofenac 75 mg given intramuscularly in efficacy and tolerability in the management of postoperative pain following mastoidectomy surgery.

KEYWORDS – Postoperative pain, Lornoxicam, Diclofenac, Mastoidectomy surgery.

INTRODUCTION

Pain in postoperative period is associated with any type of surgery. The severity of the postoperative pain is related to the type of the surgery and relief from pain is an essential component of postoperative patient care. Postoperative pain sensation is due to the surgical trauma that occurs during manipulation of tissues[1].

Mastoidectomy surgery causes continuous distress to patient hampering recovery time and affects the outcome of the patient. Postoperative pain being not relieved promptly increases the stress response of the immune system leading to delayed wound healing and prolonged hospitalisation[2]. Early and effective postoperative pain relief can reduce the postoperative pain related complications and decrease the duration of hospitalisation by enabling early ambulation[3].

It has been observed that postoperative pain in 20 to 40% of patients is of moderate intensity and pain in 50-70% is severe in nature[4]. Drugs used in the management of postoperative pain must be effective and safe with minimal adverse effects[1]. In the management of postoperative pain, opioids are the main stay after surgical procedures, however it has many adverse effects like respiratory depression, nausea, vomiting , constipation. On the other hand non-steroidal anti-inflammatory drugs (NSAIDS) are used in the postoperative pain management to avoid the adverse effects associated with the opioids[5].

Lornoxicam is a nonselective NSAID and it belongs to oxicams with analgesic and anti-inflammatory properties. Besides its inhibitory effects on cyclooxygenase (COX1 and COX2) it also increases endogenous dinorphin and beta endorphin levels promoting central analgesic and anti-inflamatory effects[4]. Lornoxicam has pharmacokinetic and pharmacodynamic properties similar to piroxicam and it is as effective as morphine, pethidine and tramadol in managing pain after major surgeries[5].

Lornoxicam has rapid onset of action when compared to other oxicams and has short halflife[1]. Lornoxicam has better safety profile than diclofenac with regards to renal and hepatic function tests and it has been used successfully in the management of postoperative pain[6].

Diclofenac sodium is a cyclooxygenase inhibitor and has been used in the management of postoperative pain for many years. It accumulates in the inflamed tissue and the concentration are maintained higher in plasma for many hours and its active metabolite acts as an analgesic[7].

There is lack of clinical trials comparing Lornoxicam and Diclofenac in the management of postoperative pain. Thus the present study was done to evaluate the analgesic efficacy and safety of Lornoxicam when compared to Diclofenac in postoperative patients following Mastoidectomy surgery.

REVIEW OF LITERATURE

The management of pain always remains a challenge to the clinicians[8]. A revolution has occurred in the management of acute post-operative pain during the past two decades[9]. Inspite of understanding the pathophysiology of pain it is difficult to control pain[8]. Pain perception is the series of electrochemical events following tissue damage or injury. Pain can be effectively relieved in 90% of patients but only 20% of patients achieve effective pain relief[10].

Definition of pain: Pain is defined by International Association for the study of pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of tissue damage or both[11].

The purpose of pain is protective mechanism for the body and it occurs whenever any tissues are being damaged[12]. Pain is one of nature's earliest signs of morbidity and it stands pre-eminent among all the sensory experiences by which humans judge the existence of disease with in themselves[13].

Pain can be classified as acute pain, chronic pain and malignant pain. Acute pain is due to injury, surgery, illness, trauma or painful medical procedure. Pain lasts for short period and disappears after treating the underlying cause or after adequate time for healing. Chronic pain is a persistent pain not associated with malignancy or acute pain caused by trauma or surgery. Malignant pain is associated with carcinoma[14].

HISTORY OF PAIN

In prehistoric period there was belief that intrusion of objects or spirits in to the body is the source of unpleasant and distressful experience. The chinese canon of medicine 2600BC gave major importance to the heart, presumed to regulate life and the brain was ignored. Aristotle believed touch to be closely related to pain and he recognized the relationship between tissue injury and pain. Herophilus 335-280BC proposed brain to be organ of consciousness and sensation. Galen 130-280 proposed that brain is the paramount organ for consiousness and sensation.

Early in Rennaissance, Lenonardo da vinci appreciated the role of peripheral nerves in carrying messages from to and from the body. Physicians in 3rd century BC proposed nerves have specific functions. Charles Bell (1774-1842) proposed the differences in function between the dorsal and ventral roots of the mammalian spinal cord. Francois Megendie proposed the function of spinal roots. Bell and Megendie together discovered the function of spinal cord and pain mechanism.

In 1858 Moritz Schiff student of Megendie described effects of spinal cord lesions in dogs and cats and proposed separate spinal pathways for tactile stimulation, movement detection, pain and temperature sensation[15].

THEORIES OF PAIN

For more than centuries the views on nature of pain sensation have been dominated by many theories.

1. **Specificity theory** – This theory was given by Von Frey. He declared that the skin consisted of a mosaic of discrete sensory spots and that each spot when stimulated gave rise to one sensation either pain, pressure, warmth or cold. In his view each of these sensations had a distinctive end organ in the skin and each stimulus specific end organ was connected by its own private pathway to the brain.
2. **Summation theory** - This theory was given by Gold Scheider according to him there were no distinctive pain receptors and the sensation of pain was the result of the summation of impulses excited by pressure or thermal stimuli applied to the skin originally called as intensivity theory, later known as the pattern or summation theory.
3. **Gate control theory** – In 1965 Melzack and Wall propounded the most important " gate control " theory, they observed that in decerebrate and spinal cats, the peripheral stimulation of large myelinated fibers produced a negative dorsal root potential and stimulation of small C pain fibers caused positive dorsal root potential. They postulated that these potentials were reflection of presynaptic inhibition or excitation which modulated the activity of secondary transmitting neurons in the dorsal horn. This modulation was mediated through inhibitory cells. They also emphasised that pain impulses from dorsal horn must be

under the control of descending system of fibers from brainstem, thalamus and limbic lobes.[16,17,18]

CLASSIFICATION OF PAIN

1. **Nociceptive pain**: It is due to tissue irritation, impending injury or actual injury. Nociceptors are activated in the affected area and transmits signals via the peripheral nerves and spinal cord to the brain, activating the complex spinal reflex (withdrawl) followed by perception, cognition and affective response and voluntary action .Nociceptive pain is time limited and respond well to treatment with opioids.
2. **Neuropathic pain**: It is due to injury or malfunction of the nervous system in the peripheral or central nervous system. Pain persists for months or years beyond apparent healing of any damaged tissue. Neuropathic pain is chronic and responds less to treatment with opioids.
3. **Psychogenic pain**: It is due to psychological factors leading to exaggerated or histrionic presentation of the pain problem.
4. **Mixed category pain**: It is caused by complex mixture of nociceptive and neuropathic factors .Initial nervous system dysfunction or injury trigger the neural release of inflammatory mediators and subsequent neurogenic inflammation.

Postoperative pain can also be divided in to acute pain and chronic pain. Acute pain is experienced immediately after surgery up to seven days. Chronic

pain lasts for more than three months after surgery. Acute and chronic pain arise from cutaneous deep somatic or visceral structures.

It is important to distinguish between first pain and second pain .First pain is sharp and pricking. It localises to well defined part of the body surface mediated by specific nociceptors. Second pain is dull aching poorly localized due to stimulation of receptors in the main tissues[12].

PHYSIOLOGY OF NOCICEPTION

The purpose of pain is mainly protective mechanism for the body it occurs whenever tissues are damaged. Pain is classified in to fast pain and slow pain.

a. Fast pain – It is also called as sharp pain, pricking pain, acute pain, electric pain. Pain is felt within 0.1 sec after the pain stimulus is applied. Felt when skin is cut with a knife or needle stick in to the skin.[12] This activity is due to the activation of $A\delta$ pain fibers[11]

b. Slow pain – It is also called as slow burning pain, aching pain, throbbing pain, nauseous pain, chronic pain. Pain begins after one second or more and then increases slowly over many seconds and sometimes even minutes. Pain is due to tissue destruction. It occurs in skin and in any deep tissue or organ.[12] It is due to activation in the C pain fibers[11].

NOCICEPTORS:

Main organs in the periphery like skin and subcutaneous structures, joints and muscles possess sensory receptors activated by noxious insults. The nociceptors are simply the free nerve endings of primary sensory neuron. Three main class of nociceptors are thermal, mechanical, polymodal and the fourth class silent nociceptors.

Thermal nociceptors – It is activated by extremes of temperature >45 C or < 5 C. They are the peripheral nerve ending of small diameter , thinly myelinated Aδ axons.

Mechanical nociceptors – It is activated by intense pressure applied to the skin.They are also the nerve endings of Aδ axons.

Polymodal nociceptors – It is activated by high intensity mechanical , chemical or thermal stimuli .They are found at the ends of small diameter in myelinated C axons.

Silent nociceptors – They are found in the viscera not activated by noxious stimuli . Inflammation and various chemical agents reduce the firing threshold[19].

The membrane of the nociceptor contains receptors that convert the thermal, mechanical or chemical energy of noxious stimuli in to depolarizing electric potential. One such receptor is a member of large family called Transient Receptor Potential (TRP) ion channel.

TRPV1 expressed by nociceptive neurons and mediate the pain producing actions of capsaicin, the active ingredient of hot peppers and many other pungent chemicals . TRPV1 channel is also stimulated by noxious stimuli, thermal stimuli and reduction in pH.

TRPV2 channel is expressed in Aδ fiber terminals and inactivated by very high temperature. TRP M8 channel is activated by low temperature and by chemicals like menthol.

Nociceptors selectively express tetrodotoxin resistant Na channel. SCN9A Na channel gene plays an important role in perception of pain. Mutation of the gene reveal rare pain insensitive individuals.

Nociceptors express an ionotropic purinergic receptor PTX3 that is activated by adenosine tri phosphate released from peripheral cell after tissue damage. Mas related G protein coupled receptor family are activated by peptide ligands that sensitise nociceptors to other chemicals released in their local environment.

The uncontrolled activation of nociceptors is associated with several pathological conditions[20 21]. Allodynia and hyperalgesia are two common pain states that reflect changes in nociceptor activity.

Hyperalgesia – Increased amount of pain associated with mild noxious stimulus. Patient report persistent pain in the absence of sensory stimuli.

Allodynia – Pain associated with non-noxious stimulus or spontaneous pain without any precipitating stimulus[22]

PERSISTENT PAIN

Persistent pain can be subdivided in to two classes

a. Nociceptive pain – It is due to activation of nociceptors in skin or soft tissues in response to tissue injury.

b.Neuropathic pain – It is due to direct injury to nerve in peripheral or central nervous system accompanied by burning or electric sensation.

Anesthesia dolorosa –It is a phenomenon in which pain occur without peripheral stimulus[20].

PATHWAY OF PAIN

Sense organ for pain are the naked nerve endings found in every tissues of the body. Pain impulses are transmitted to the CNS by two fibre system.

1. Small Myelinated typeA delta fibers 2-5μm in diameter conduct at the rate of 12-30m/s.
2. Unmyelinted typeC fibre 0.4 – 1.2 μm in diameter conduct at the rate of 0.5 – 2m/sec

Both the fibers end in the dorsal horn, Aδ in lamina 1 & 5 and dorsal root C fibers terminate in lamina 1&2. Synaptic transmitter secreted by primary afferent fibers for mild pain is glutamate and for severe pain is substance P[11].

The primary afferents are classified by their diameter, degree of myelination and conduction velocity. Aδ and C fibers are primary nociceptors. Primary afferent nociceptors respond to stimuli like a pinch, changes in pH, acidic environment, chemical irritants, ATP, serotonin, bradykinin and histamine[19] .

MODULATION IN NOCICEPTIVE PATHWAY :

There is a dual pathway for transmission of pain signals in to the brain. The two pathway for two different types of pain are

1. Acute sharp pain pathway
2. Slow chronic pain pathway

Peripheral pain fibers - Fast and slow signals are transmitted in peripheral nerves to the spinal cord, type Aδ for acute sharp pain signals and type C fibers for slow chronic type pain signals. On entering spinal cord from dorsal spinal root the pain fibers ascend or descend.

Acute sharp pain pathway – The fast type A δ pain fibers terminate at dorsal horns in lamina 1 and 5 and excite the second order neuron .Second order neuron send long fibers immediately to the opposite side of the cord in the anterior commissure and the to the brain in the lateral division of anterolateral sensory pathway.

After entering the brain stem, three quarters to nineteenths of all pain fibers terminate in the reticular formation of the medulla, pons and mesencephalon. . From these areas higher order neurons are transmitted to the thalamus, hypothalamus and areas of diencephalon and cortex of the brain.

Small portion of fast acute pain fibers terminate in ventrobasal complex and posterior nuclear group of thalamus along with sensory fibers from dorsal column lemniscal pathway. From there signals are transmitted to thalamus and somatosensory cortex. Signal to cortex is important for localizing the pain

Slow chronic pain pathway – Type C fibers transmit slow pain signals terminate in lamina 2 and 3 of the dorsal horn called substansia gelatinosa . One or more additional short fibre neurons terminate in lamina 5. These fibers pass through anterior commissure to the opposite side and then upward to the brain via the lateral division of anterolateral sensory pathway. Few of these fibers do not pass ipsilaterally to the brain. In the brain terminate entirely in the reticular formation of the brain stem and in to the intra laminar nuclei of the brain stem and then finally to the cerebral cortex of the brain.

Surgical incision produces tissue injury with consequent release of histamine and inflammatory mediators like peptide (bradykinin) , lipids (prostaglandin), neurotransmitter (serotonin), neurotrophins (nerve growth factor). The release of inflammatory mediators activates peripheral nociceptors which initiate transduction and transmission of nociceptive information to the central nervous system. Noxious stimuli are transduced by peripheral

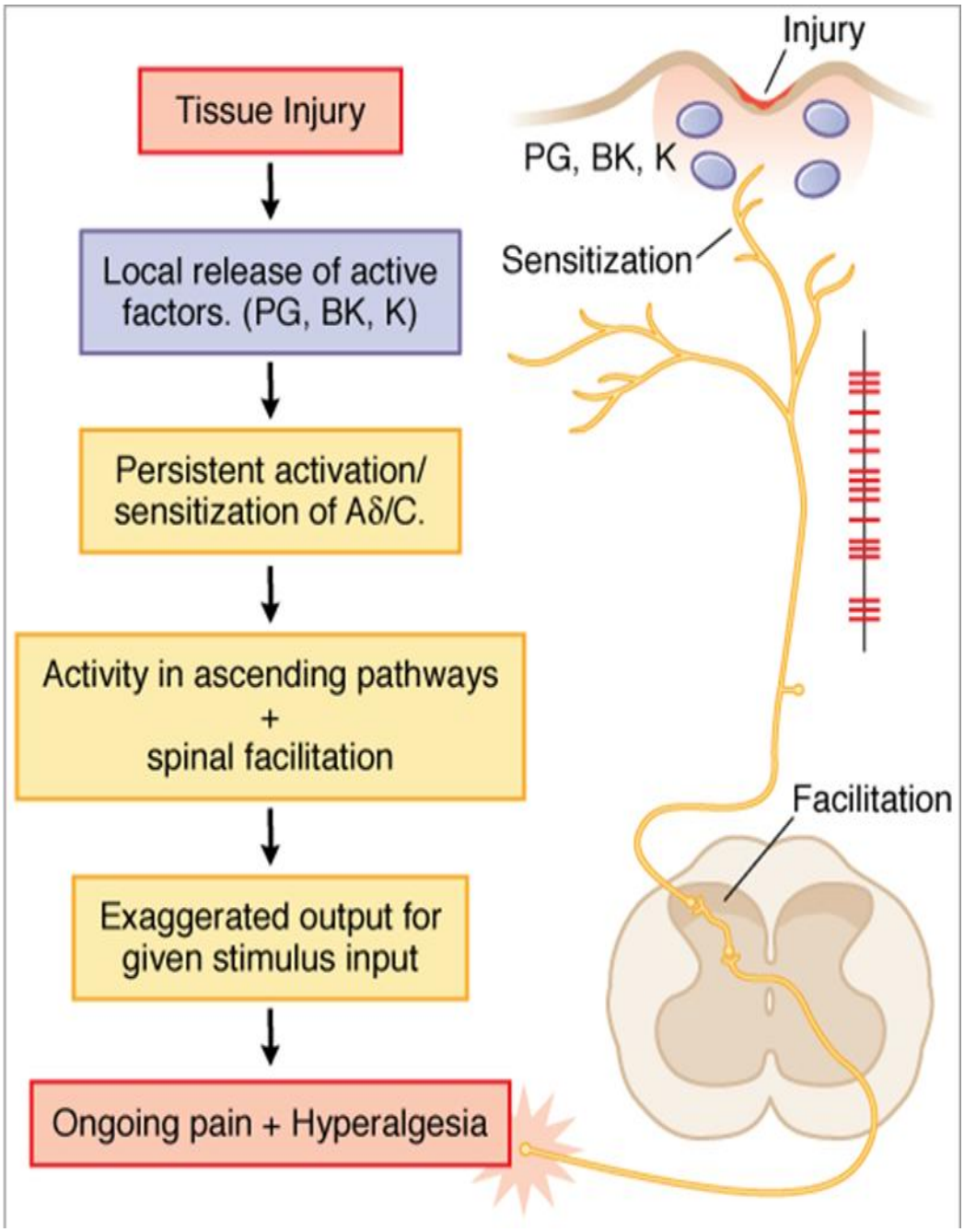
nociceptors and transmitted by Aδ and C nerve fibre from peripheral visceral and somatic sites to dorsal horn of spinal cord where integration of peripheral nociceptive and descending inhibitory modulatory input (serotonin, nor epinephrine, GABA and enkephalin) or descending facilitatory input (cholecystokinin, excitatory aminoacid, dynorphin) occurs. Some impulse pass to ventral and ventrolateral horns to initiate spinal reflex responses. Other signals are transmitted to the higher centre through the spinothalamic and spinoreticular tracts where they produce cortical response to generate the perception of pain[23].

SENSITISATION

When intense repeated or prolonged stimuli are applied to damaged or inflamed tissue the threshold for activating primary afferent nociceptors are lowered and the frequency of firing is higher for all intensities of the stimuli .Inflammatory mediators like prostaglandins, leukotrines, bradykinin, nerve growth factor contribute to sensitization[19]

FIGURE – 1

FLOW DIAGRAM OF TISSUE INJURY EVOKED NOCICEPTION[24]



PAIN CONTROL SYSTEM IN THE BRAIN AND SPINAL CORD

The degree to which each person reacts to pain varies, due to the capability of brain to control the degree of input of pain signals to the nervous system by activation of pain control system called an analgesia system.

It consist of three major components and other accessory components

1. Periaqueductal grey area of the mesencephalon and upper pons surrounding the aqueduct of sylvius neurons. From here signals are sent to Raphe Magnus nucleus.
2. Raphe Magnus nucleus is a thin midline nucleus located in the lower pons and upper medulla. From here signals are transmitted down to spinal cord.
3. Pain inhibitory complex located in the dorsal horn of the spinal cord, at this point pain signals can be blocked before they are relayed to the brain.

Electrical stimulation in the periaqueductal grey especially the periventricular nuclei in the hypothalamus and to a lesser extent the medial forebrain bundle in the hypothalamus can suppress pain. The main neurotransmitter substance involved in analgesia system is encephalin and serotonin.

Nerve fibers derived from the periventricular nuclei and periaqueductal grey secrete encephalin at their nerve ending. These fibers end in the Raphe magnus nucleus release enkephalins. Fibers originating from this nucleus

terminate in the dorsal horn of the spinal cord secrete serotonin at their endings .The serotonin in turn acts on local cord neurons that secrete enkephalins. Enkephalins produce presynaptic inhibition of incoming pain fibers to laminae 1 through 5 in dorsal horns.

Analgesia system can block pain signal at the initial entry point to the spinal cord and also at other points in the pain pathway especially in the reticular nuclei in the brain stem and in the intralaminar nuclei of the thalamus. Pain analgesia system is capable of blocking both fast sharp type pain and slow burning aching type pain[11,12].

In a study it was discovered that injection of extremely minute quantities of morphine in to periventricular nucleus around the third ventricle of the diencephalon or in to periaqeductal grey of brain stem produce extreme degree of analgesia. Subsequent studies have shown that morphine acts at other points in the analgesia system including Raphe Magnus nucleus and dorsal horns of spinal cord[12].

A. ENDOGENOUS OPIOIDS

An agent found with in the brain that act through an opioid receptor is an endogenous opioid . Principal endogenous opioid peptides are

1. Enkephalin
2. Endorphins
3. Dynorphins
4. Endomorphins

5. Nociceptin peptide

Common properties of endogenous opioids

Derived from large precursor protein preproopiomelanocortin (POMC), Preproenkephalin, preprodynorphin encoded by corresponding gene.

Each precursor is subject to complex clevages by trpsin like enzymes at sites designated by pairs of dibasic aminoacids to post translational modifications resulting in synthesis of multiple peptides, some of which are active.

Most opioid share the common amino terminal sequence of Tyr – Gly – Gly- Phe- Met or Leu followed by various C terminal extensions yielding peptides ranging from a few to many residues .

a. <u>Proenkephalin</u> – It contains multiple copies of metenkephalin and single copy of leuenkepalin. They are present in areas of the central nervous system and are related to the

a. Processing of pain information for example lamina 1 and 2 of spinal cord, spinal trigeminal nucleus and peraqueductal gray.

b. To the modulation of motor control (caudate nucleus and globus pallidus)

c. To the regulation of autonomic nervous system (medulla oblongata)

d. To neuroendocrinological functions (median eminence)

b.Prodynorphin – It contains three peptides of differing lengths that begin with leuenkephalin sequence, Dynorphin-A, Dynorphin-B and Neoendorphin. They are distributed widely in neurons and lesser extent in the astrocytes throughout brain and spinal cord.

c.Endorphin – β endorphin is a potent opioid agonist derived from cleavage of betalipotropin generated by proteolytic cleavage of POMC. POMC distribution is limited with in central nervous system , in the arcuate nucleus of the hypothalamus and nucleus tractus solitaries and also in the anterior and intermediate lobes of pituitary and pancreatic islet cells .

d.Endomorphins– It is a recently identified peptide endomorphin 1 and endomorphin 2 they have an atypical structure and selective towards μ opioid receptor.

e.Nociception peptides (orphanin FQ) – They are Present in the neurons of cortex , hippocampus , brainstem , hypothalamus, raphe nuclei and periaqueductal grey of the brain and are also present in the spinal cord[24].

B. OPIOID RECEPTORS

Opioid systems are critical in the modulation of pain behavior and nociception. Opioid peptides and their receptors are expressed throughout the nociceptive neural circuit. Opioid receptors were pharmacologically and genitically identified over decades ago. Opioid receptors are targeted for treatment of pain thousands of years ago.

Subtypes of opioid receptor

Mu - μ , delta $-\delta$ and kappa $-$ ƙ, least characterized receptor is opoid receptor like (ORL 1). All the receptors are G protein coupled and activate inhibitory G proteins.

Opioid receptors are expressed in pain modulating descending pathway which include medulla, locus coeruleus and periaqueductal grey area. They are also expressed in limbic, midbrain and cortical structures. The activation of opioid receptors at these locations directly inhibit neurons which in turn inhibit spinal cord pain transmission. All four receptors are seven membrane spanning protein that couple to inhibitory G protein. After the activation of opioid receptor by endogenous or exogenous opioids the G α and G β subunits dissociate from one another and acts on various intracellular effector pathway. When activated all the four receptors cause reduction in calcium current that are sensitive to P/Q type ,N type and L type[25].

MEDIATORS OF PAIN

Acute inflammation is a rapid host response that deliver leucocytes and plasma proteins, antibodies to site of tissue injury. Acute inflammation has three major components

1. Alterations in vascular caliber that lead to an increase in blood flow
2. Structural changes in the microvasculature that permit plasma proteins and leucocytes to leave the circulation

3. Emigration of the leucocytes from microcirculation and their activation to eliminate offending agent.

General principles of Mediators of inflammation

a. Mediators are generated either from cells or from plasma proteins -The major cell that produce mediators of acute inflammation are platelets, neutrophils, monocytes/macrophages. Cell derived mediators are sequestered in intracellular granules and rapidly secreted by granule exocytosis in response to a stimulus.
b. Active mediators produced in response to stimuli – The stimuli are the microbial products , substance released from necrotic cells and the proteins of the complement , kinin and coagulation systems.
c. One mediator can stimulate the release of other mediators – cytokine and Tumor Necrosis Factor (TNF) act on endothelial cells to stimulate the production of another cytokine IL-1 and many chemokines.
d. Once activated and released from the cell most of the mediators are short lived they quickly decay or inactivated by enzymes or scavenged or inhibited[26].

Mediators of inflammation are classified as follows

1. **Cell derived Mediators**
2. **Plasma protein–derived mediators**

I . CELL DERIVED MEDIATORS

a. Vasoactive amines – Histamine and Serotonin

- **Histamine** – It is a principal mediator of immediate transient phase of increased vascular permeability .They are stored as preformed molecules in cells and are the first mediators to be released during inflammation. The richest source of histamine is mast cells and are also found in blood basophils and platelets. Histamine is released from the mast cells by mast cell degranulation in response to

1. Physical injury, trauma, cold or heat
2. Binding of antibodies to mast cells
3. Complement fragments called anaphylatoxins C3a and C5a
4. Histamine releasing proteins derived from leucocytes
5. Neuropeptides (substance P)
6. Cytokine (IL-1,IL-8)

Histamine cause immediate vasodilation of arterioles and increased permeability of venules.

- **Serotonin** – It is present in platelets and neuroendocrine cells preformed vasoactive mediator

b. <u>Arachidonic acid (AA) metabolite</u> – Prostaglandins , leukotrienes and lipoxins

When cells are activated by a stimuli like microbial products and various mediators of inflammation, membrane arachidonic acid is converted to prostaglandins and leukotrienes by action of various enzymes. Arachidonic acid is a 20-carbon polyunsaturated fatty acid derived from dietary sources or by conversion from the essential fatty acid linoleic acid and are esterified in membrane phospholipids. Mechanical, chemical, and physical stimuli or other mediators (C5a) release arachidonic acid from membrane phospholipids through the action of cellular phospholipase A2. Arachidonic acid derived mediators, also called eicosanoids, are synthesized by two major classes of enzymes :

1. Cyclooxygenases that generate prostaglandins

2. Lipoxygenases that produce leukotrienes and lipoxins.

Eicosanoids bind to G protein–coupled receptors on many cell types and can mediate the process of inflammation.

- **Prostaglandins (PGs)** -They are produced by mast cells, macrophages, endothelial cells, and other cell types involved in the vascular and systemic reactions of inflammation. They are produced by the actions of two cyclooxygenases, COX-1 and COX-2.

Prostaglandins are divided based on structural features in to PGD, PGE, PGF, PGG, and PGH and a subscript numeral (e.g., 1, 2), which indicates the number of double bonds in the compound. The most important PG in inflammation are PGE2, PGD2, PGF2α, PGI2 (prostacyclin), and TxA2 (thromboxane).

PGE2 – It is widely distributed and causes vasodilation and increases the permeability of post capillary venules. It makes skin hypersensitive to painful stimuli.

PGD2 –It is a chemo attractant for neutrophils

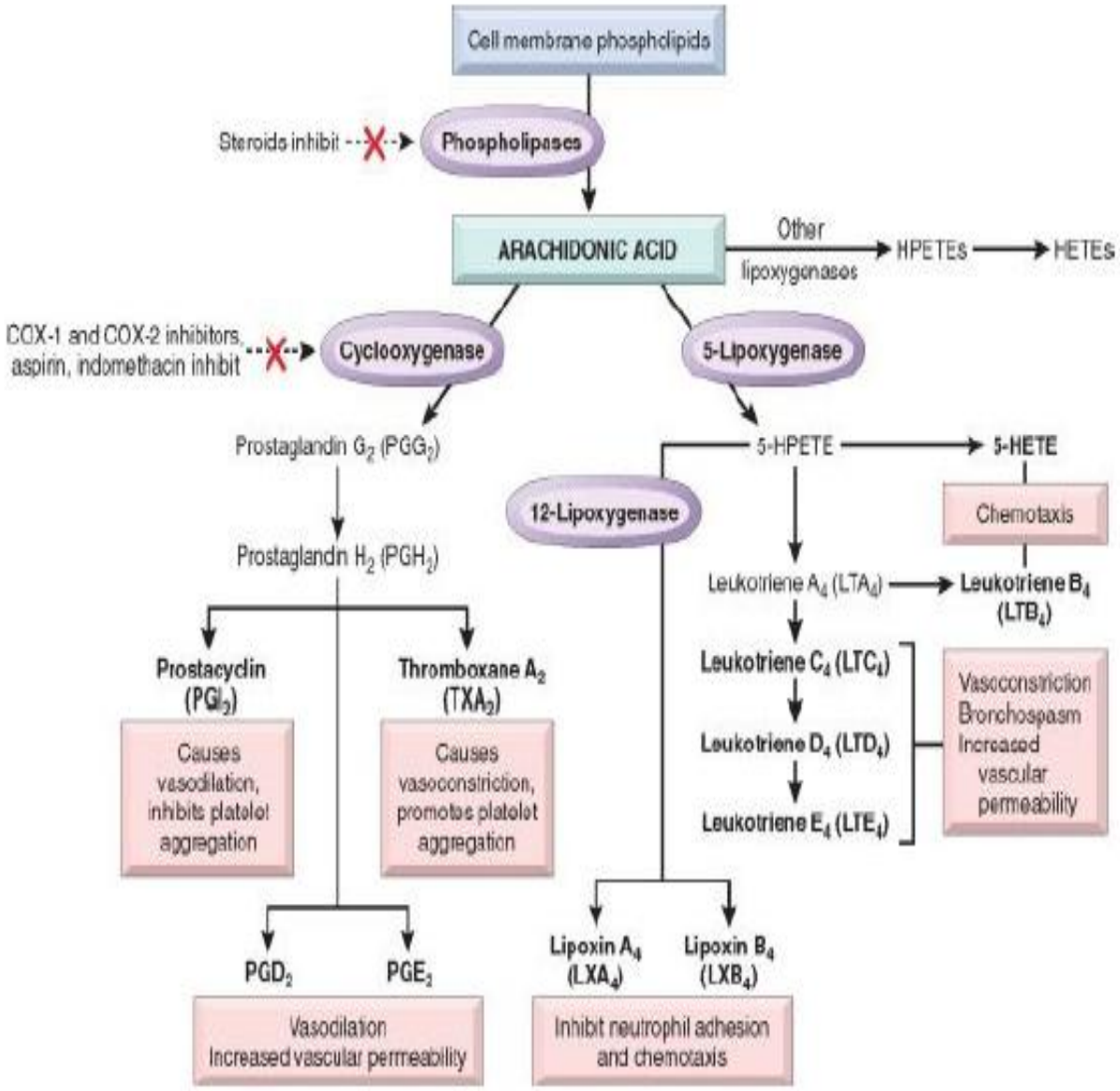
PGF2α –It Produce uterine contraction , bronchial smooth muscle contraction

PGI2 – It Produce vasodilation , potent inhibitor of platelet aggregation .

TXA2 – It is a potent platelet aggregating agent and vasoconstrictor and it is rapidly converted to inactive form TXB2.

FIGURE – 2

GENERATION OF ARACHIDONIC ACID METABOLITES AND THEIR ROLES IN INFLAMMATION[26]



- **Leukotrienes** – The lipoxygenase enzyme is responsible for the production of leukotrienes secreted by leukocytes. There are three different lipoxygenases, 5-lipoxygenase is predominant in neutrophils that converts arachidonic acid in to 5-hydroxyeicosatetraenoic acid and it is chemotactic for neutrophils and is the precursor of the leukotrienes.

LTB4 - potent chemotactic agent and activator of neutrophils, causing aggregation and adhesion of the cells to venular endothelium, generation of Reactive oxygen species, and release of lysosomal enzymes.

LTC4, LTD4, LTE4 - The cysteinyl containing leukotrienes cause vasoconstriction, bronchospasm and increased vascular permeability.

- **Lipoxins** - They are also generated from arachidonic acid by the lipoxygenase pathway, but unlike prostaglandins and leukotrienes, they are inhibitors of inflammation. The main action of lipoxin is to inhibit leucocyte recruitment and cellular component of inflammation. They inhibit neutrophil chemotaxis and adhesion to endothelium and they are endogenous negative regulators of leukotrienes and thus produce resolution of inflammation.

C.<u>Other mediators of inflammation</u>

- **Platelet-Activating Factor (PAF) -** Phospholipid-derived mediator that causes platelet aggregation and have multiple inflammatory effects
- **Reactive Oxygen Species** -Oxygen-derived free radicals released from leukocytes after exposure to microbes, chemokines, and immune complexes.
- **Nitric Oxide (NO)** –It is a factor released from endothelial cells that caused vasodilation and are called as endothelium-derived relaxing factor. NO is a soluble gas that is produced by macrophages and neurons in the brain.NO is synthesized from L- Arginine by the enzyme nitric oxide synthase (NOS).
- **Cytokines and Chemokines** – cytokines are proteins produced by lymphocytes, macrophages and by endothelial, epithelial, and connective tissue cells. Cytokines involved in acute inflammation are IL-1, IL- 6, TNF.
- **Lysosomal Constituents of Leukocytes** - Neutrophils and monocytes contain lysosomal granules, when released produce the inflammatory response. Neutrophils have two types of granules, the smaller specific granules contain lysozyme, collagenase, gelatinase, lactoferrin, plasminogen activator, histaminase, and alkaline phosphatase and the larger azurophil granules contain myeloperoxidase, bactericidal factors (lysozyme), acid hydrolases, elastase, cathepsin G, nonspecific collagenases and proteinase.

- **Neuropeptides** - They are secreted from sensory nerves and various leukocytes, and play an important role in the initiation and propagation of an inflammatory response. Substance P and Neurokinin A belong to a family of tachykinin. Neuropeptides are produced in the central and peripheral nervous systems. Substance P has biologic functions like transmission of pain signals, regulation of blood pressure, stimulation of secretion by endocrine cells, and increasing vascular permeability. Sensory neurons also produce pro-inflammatory molecules like calcitonin-related gene product.

II. PLASMA PROTEIN–DERIVED MEDIATORS

A variety of inflammatory response are mediated by plasma proteins that belong to three interrelated systems: the complement, kinin, and clotting systems.

a. **Complement System** - It consists of more than 20 proteins that function in both innate and adaptive immunity for defense against microbial pathogens.
b. **Coagulation and Kinin Systems** – Inflammation and blood clotting are interwined with each promoting the other . Inflammation increases the production of several coagulation factors and makes the endothelial surface pro-thrombogenic, and inhibits anticoagulation and there by promoting clotting.
c. **Kinins** – They are vasoactive peptides derived from plasma proteins called kininogens by action of protease , kallikriens . The active form of

factor XII, factor XIIa, converts plasma prekallikrien in to an active proteolytic form, kallikrien. which cleaves high molecular weight kininogen to bradykinin. Bradykinin increases vascular permeability and produce contraction of smooth muscle and also dilation of blood vessels and produce pain when injected to skin. The action of bradykinin is short-lived as it is quickly inactivated by an enzyme kininase[27,28,29,30].

SYSTEMIC RESPONSES TO PAIN

Acute pain is associated with neuroendocrine stress response and it is proportional to pain intensity. Sympathetic activation increases the sympathetic tone and releases catecholamines from adrenal medulla.

- **Cardiovascular effects** – Includes hypertension, tachycardia, myocardial irritability, increased systemic vascular resistance Pain can aggravate or precipitate myocardial ischemia due to increase in myocardial oxygen demand.
- **Respiratory effects** – Increase in minute ventilation as there is increase in total body oxygen consumption and carbondioxide production. Prolonged bed rest or immobilization due pain produce change in pulmonary function.
- **Gastrointestinal and urinary effects** – Increased sympathetic tone increases sphincter tone and decreases urinary and intestinal motility . Hyper secretion of gastric acid promote stress ulcer. Nausea, vomiting and constipation are common.

- **Endocrine effects** – Stress increases catabolic hormones and decreases anabolic hormones . Increase in cortisol with increase in renin angiotensin and antidiuretic hormone results in sodium and water retention .
- **Hematological effects** – Stress increases platelet adhesiveness, reduced fibrinolysis and hypercoagulability .
- **General sense of well-being** – Anxiety , sleep disturbance occurs[31].

MEASUREMENT OF PAIN

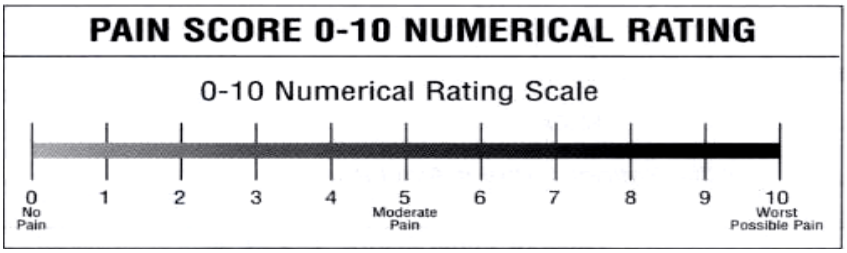
Accurate assessment of acute pain is essential for the development of an effective pain management plan[32]. Patients self-report is a reliable indicator of pain , as pain is a subjective experience and it is the patients perception that is documented[32]. Pain is assessed as follows

- At regular time intervals consistent with surgery type and severity of pain
- With each new report of pain
- At suitable interval after each analgesic intervention[33] .

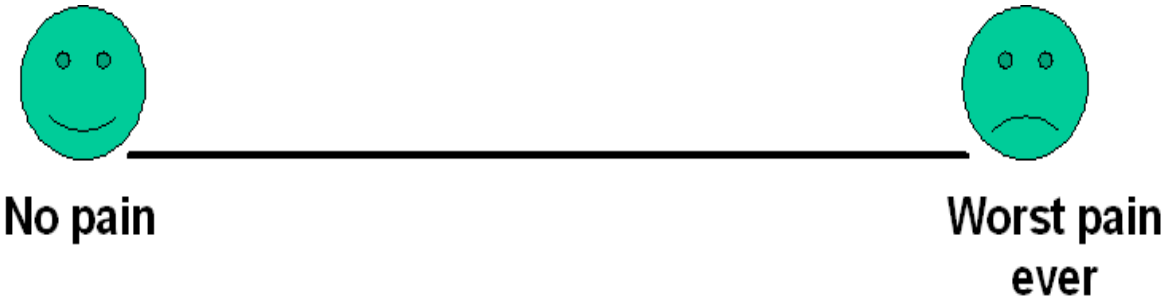
Pain assessment tools should be reliable for the patient population. Self - reported measurement tools can be classified as

I. UNIDIMENSIONAL TOOLS

a. **Numeric rating scale (NRS)** - It is a segmented numeric version of the visual analog scale (VAS) in which the patient selects a whole number (0–10 integers) reflects the intensity of their pain .



b. **Visual analog scale (VAS)** - It is a continuous scale comprised of a horizontal (HVAS) or vertical (VVAS) line of 10 centimeters (100 mm) in length. For pain intensity score of 0 is considered as "no pain"and score of 10 in 10 cm scale is considered as "pain as bad as it could be" or "worst imaginable pain". Patient is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity. Using a ruler, the score is determined by measuring the distance on the 10-cm line. The results are interpreted as , no pain (0–0.4 cm), mild pain (0.5–4.4 cm), moderate pain (4.5–7.4 cm), and severe pain (7.5–10 cm)[32,34].



c. <u>Verbal rating scale (VRS)</u> - It is the oldest and the simplest form of pain measurement tool . In clinical practice, four-descriptor verbal rating scale measuring pain is used with words none ,mild, moderate, and severe pain. The five- word scale consists of mild, discomforting, distressing, horrible and excruciating.

d. F<u>aces pain scale – revised (FPS-R)</u> - It is scored 0-10 or 0-5 . The face pointed to left shows no pain and faces show more and more pain from left to right. the patient is asked to point the face how much they are hurt[35] .

e. <u>Wong-Baker Faces pain rating scale</u> - It is an ordinal out- come measure with limited number of categorical responses. This consists of six facial expressions and it is explained to the patients that each face is for a person who feels happy, face 0 is very happy doesn't hurt at all., face 1 hurts just a little bit, face 2 hurts a little more , face 4 hurts a whole more , face 5 is hurts as much as you can imagine [35,36,37].

II. **Multidimentional tools**

a. **Mcgill pain questionnaire (MPQ) -** Multidimensional pain questionnaire to measure the sensory, affective and evaluative aspects of pain and pain intensity in adults with chronic pain.

b. **Short- form Mcgill pain questionnaire (SF-MPQ) -** It is a shorter version of the MPQ and it is a multidimensional measure of perceived pain in adults with chronic pain.

c. Quantitative sensory testing (QST) - Non- invasive form of somatosensory testing that provides information of the afferent pain pathway from receptor to brain[32,33].

MANAGEMENT OF POST OPERATIVE PAIN

Pain management are targeted at the preoperative period. Preemptive analgesia involves preoperative administration of analgesics that helps to reduce the consequences of afferent nociceptive neurotransmission during surgery and thereby decreasing postoperative pain. Preventive analgesia involves prevention of central sensitization by blocking the neural transmission of all noxious perioperative stimuli arising from the time of incision to till wound healing.

Intraoperative approaches include neuraxial analgesia, continuous local anesthetic wound infusion, intravenous acetaminophen and intravenous ketamine. Pain management approaches during the postoperative period is the traditional pharmacological approach which include oral or intravenous

administration of opioids and oral administration of acetaminophen or NSAID[38].

a. **Pharmacological management of pain**
    - Opioid analgesics
    - Non-opioid analgesics non-steroidal anti-inflammatory drugs
b. **Non - pharmacological management of pain**
    - Psychological interventions
    - Physical therapy
    - Acupuncture
    - Electrical stimulation

A. PHARMACOLOGICAL MANAGEMENT OF PAIN

a. OPIOID ANALGESICS

There are three types of opioid receptors are MOR (mu- μ), DOR (delta -δ) and KOR (kappa- κ). Based on their methods of stimulation, opioids can be divided into full agonists, partial agonist, agonist-antagonist. Full agonist is characterised by relative selectivity for μ receptors, similar to morphine, partial agonists shows partial agonism mainly for μ receptors, and opioids of mixed agonistic-antagonistic properties interact with more than one class of receptors and therefore it can act as agonists for one receptor and as antagonists for the other. The most important opioids used in acute pain management include morphine, oxycodone, fentanyl, nalbuphine, buprenorphine and tramadol.

Opioids commonly used for pharmacological relief of moderate to severe post-operative pain. Their doses should be tailored individually depending on the pain evaluation scores and their possible adverse side effects.

Mechanism of opioid induced analgesia

The analgesic actions of opiates after systemic delivery has actions in the brain, spinal cord, and in the periphery.

Supra spinal Actions - The microinjection of opiates through microinjection cannulae targeted at specific brain sites like mesencephalic periaqueductal gray (PAG) matter has shown that opiate agonists act on MOR, block pain behavior and the analgesic effects are reversible by naloxone.

Spinal Opiate Action - A local action of opiates in the spinal cord will depress the discharge of spinal dorsal horn neurons evoked by small but not large afferent nerve fibers. Spinal opiates reduce the release of primary afferent peptide transmitters such as substance P in the small afferents . The presynaptic action prevent the opening of voltage-sensitive Ca^{2+} channels preventing transmitter release. Opiates in postsynaptic action block the excitation of dorsal horn neurons directly by glutamate. The joint action of spinal opiates to reduce the release of excitatory neurotransmitters from C fibers and to decrease the excitability of dorsal horn neurons account for the powerful and selective effect of opiates on spinal nociceptive processing.

Peripheral Action - Direct application of opiates to a peripheral nerve produce a local anesthetic-like action at high concentrations and are not naloxone reversible[39].

- **Morphine** -It is a natural opium alkaloids obtained from the unripe seed capsules of the poppy plant, Papaver somniferum. Opioids are modestly absorbed from the gastrointestinal tract; absorption through the rectal mucosa is adequate. Lipophilic opioids are absorbed readily through the nasal or buccal mucosa and those with the greatest lipid solubility are absorbed transdermally. It is widely used for spinal delivery to produce analgesia though a spinal action. One-third of morphine in the plasma is protein-bound after a therapeutic dose. Morphine does not persist in tissues, and 24 hours after the last dose, tissue concentrations are low and are metabolized by glucuronide conjugation and two major metabolites formed are morphine-6-glucuronide and morphine-3-glucuronide. It is eliminated by glomerular filtration as morphine-3-glucuronide[39]. Morphine is used with caution in individuals with advanced kidney failure because of the possible accumulation of its active metabolite (morphine-6-glucuronide), which can cause respiratory failure.
- **Oxycodone** -The drug is available in intravenous, oral and other forms. The combination of this drug in its intravenous controlled-release form acts immediately. Oxycodone has two-phase absorption model, initial rapid absorption the first phase of action occurs after approximately 40

min this is followed by slow drug release over 12 hours at the constant serum concentration of the analgesic that is being maintained. Due to this action, oxycodone can be included in the group of potent drugs used for post-operative pain relief. Oxycodone administered orally is roughly twice as strong as oral morphine but the intravenous route of opioid administration during the first post-operative phase, with the possibility of changing to oral administration, is ideal for severe post-operative pain management. Oxycodone and other opioids of similar analgesic action are commonly used for the therapy of moderate-to-severe pain when there is fear of complications associated with the supply of NSAIDs.

- **Fentanyl -** It is a synthetic opioid. Its action is 50– 80 times greater than that of morphine. It has quick onset of action 10 sec after intravenous administration. The time of action after the administration of 0.1 mg is 1–1.5 hours. Fentanyl is recommended when rapid, efficacious analgesia is required .Owing to its short action, it should be used in continuous infusions. Fentanyl can be used in patients with impaired renal functions as it is metabolised into inactive metabolites in the liver.
- **Tramadol** - It is one of the weak agonist opioid receptors . It is a synthetic analogue of codeine that acts centrally. It can be used intravenously and parentrally for moderate and severe pain. The comparison of analgesic potency of tramadol with other opioids is as follows tramadol:nalbuphine 5:1; tramadol:fentanyl 979:1; tramadol:oxycodone 8:1, tramadol:morphine 10:1.

The increased analgesic action is due to inhibition of noradrenaline reuptake in neurons and an increase in serotonin release. In individuals treated with tramadol there is a risk of seizure in recommended doses. This risk increases if the recommended daily dose of 400 mg is exceeded and in patients with a history of seizures or those who are taking simultaneously serotonin and noradrenaline reuptake inhibitors, tricyclic antidepressants, anti-psychotic drugs or other agents that reduce the seizure threshold. Tramadol's capacity to produce respiratory depression is minimal therefore it is used for labour analgesia, pain relief in children, short-term and day case surgeries and after trauma. Tramadol is highly efficacious when combined with metamizole for pain management in renal or biliary colic.

- **Codeine -** It is a natural opioid and one of the major opium alkaloids. It shows low affinity to opioid receptors. Its analgesic action is provided by its active metabolite morphine. The conversion of codeine to morphine is mediated by CYP2D6. The doses for relieving pain are 30–60 mg administered every 4 h to maximum daily dose of 240 mg .

  A half-synthetic derivative of codeine is dihydrocodeine with similar pharmacological properties. Its bioavailability after oral administration is about 20% and it is metabolised in the liver by the cytochrome CYP2D6 into dihydromorphine and others.

- **Buprenorphine -** It is a partial agonist and it is similar to opioids of mixed agonistic-antagonistic properties, such as nalbuphine or

butorphanol. Agonist -antagonists have limited use for chronic pain owing to their dose-dependent, psychosis-mimetic action. Their use in patients addicted to morphine or other full MOR agonists can cause withdrawal owing to their antagonistic effects on MOR. The dose of 5–15 μg kg of parenteral buprenorphine provides analgesia comparable with that of intravenous morphine for up to 13 hours. Sublingual buprenorphine is recommended for maintaining post-operative analgesia It is useful as post-operative analgesic in patients who had been abused with opioids.

Transdermal buprenorphine is very effective due to its high solubility in fat. It is mostly recommended for chronic pain, but numerous reports from various European countries recommends its usefulness for acute pain. Transdermal buprenorphine is available in the doses of 35, 52.5 and 70 μg h-1 and the effect lasts for 3 days. The onset of action is after 12–24 hours. Buprenorphine is useful and recommended in patients with kidney failure. It is used in the elderly as it is long acting. Buprenorphine prevents hyperalgesia and hence can be used in patients with chronic pain who undergo surgeries or after trauma.

Drugs such as opioids, sedatives, hypnotics, antidepressants and others can induce or inhibit the isoenzyme of cytochrome P450 which may increase the central effects of buprenorphine. Great caution should be exercised when benzodiazepines are used simultaneously as this

combination can lead to intensified sedation, respiratory depression or even death

- **Nalbuphine -** It is a KOR agonist and MOR antagonist. As it is a MOR antagonist it prevents side effects associated with MOR stimulation like respiratory depression, addiction, euphoria, bradycardia, pruritus, immunosuppression, nausea and vomiting, impaired peristalsis, weakened muscular tone of the urinary bladder

  Nalbuphine is metabolised in the liver and excreted through the kidneys so great caution should be taken when using the drug in patients with failure of these organs. 10 mg of nalbuphine can cause respiratory depression similar to 10 mg of morphine but unlike with morphine nalbuphine shows the upper limit effect. The upper limit of respiratory depression occurs at a dose of 30 mg, and the upper limit analgesic effect is observed at 50 mg. In adults, intravenous dose used is 0.1–0.3 mg kg , without exceeding 20 mg. The maximum action is observed 2–3 minutes after intravenous administration and the dose can be repeated after 3–6 hours[39,40] .

WHO Analgesic Ladder

For mild pain – Non opioids (eg. NSAIDS, paracetamol)

For moderate pain – weak opioids (eg. Codeine) with or without non-opioids.

For severe pain – strong opioids (eg.morphine) with or without non-opoids[18].

Opioid associated complications

1. Tolerance and dependence – Repeated doses of opioids have diminishing analgesic effect, increases dose requirement needed to achieve analgesia. Physical dependence is characterized by with drawl syndrome after discontinuation of drug.

2. Addiction – it is characterized by inability to abstain consistently, impairment in behavioural control, craving, dysfunctional emotional response.

3. Respiratory system – Dose dependent respiratory depression with decreased minute ventilation via decreased respiratory rate is enhanced by CNS depressants, renal insufficiency and respiratory acidosis. Tolerance develops with repeated dosing and can be treated with naloxone.

4. Central nervous system - Sedation which is dose-dependent and may precede analgesia. Enhanced by CNS depressants and treated with naloxone.

5. GI Side Effects – Nausea vomiting are produced and are treated with serotonin and dopamine antagonists. It can produce decreased intestinal motility and constipation. Tolerance does not develop with repeated dosing and it also produce biliary spasm.

6. Pruritus – produced not due to histamine release and it is difficult to treat without reversing analgesic effects with opioid antagonists

7. Less Common Adverse Effects

a. Urinary retention - Treated with naloxone and methylnaltrexone

b. Confusion and mental status changes - Common in elderly patients

c. Bradycardia - Exacerbated by concurrent use of beta-blockers and calcium-channel blockers

d. Muscle rigidity - Seen with high doses and often requires neuromuscular blockade[41,42].

Contraindications and caution

1. Pure agonists with weak partial agonists – Pentazocine ,is a partial agonist is given with full agonist morphine , analgesia is diminished or there will be a state of with drawl so this combination should be avoided.

2. Head injury patients – respiratory depression produce carbondioxide retention which results in cerebral vasodilation, when there elevated intracranial tension it may lead to lethal alterations in brain function.

3. Pregnancy – Foetus become physically dependent in utero and manifest with-drawl symptoms in early postpartum period when given during pregnancy.

4. Patients with impaired pulmonary function – Depressant property leads to acute respiratory failure.

5. Patients with impaired hepatic or renal function – In renal impairment half-life is prolonged as they are metabolized in the liver , their use in prehepatic coma is questionable.

6. Patients with Endocrine disease – Patients with addison's disease and myxedema have prolonged and exaggerated response[41].

b. NON-OPIOID ANALGESICS NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

This group of drugs includes COX-1 and COX-2 inhibitors. The efficacy of these two types of COX inhibitors after surgeries accompanied by mild and moderate pain is comparable. In cases of classic NSAIDs used in patients at risk of gastrointestinal side effects, it is important to add a proton pump inhibitor.

Mechanism of action of NSAID

The main mechanism of action is inhibition of the enzyme cyclooxygenase which is responsible for the synthesis of prostaglandins and related autacoids like thromboxane. Prostaglandins are involved in the various physiological and pathological process of pain, fever and inflammation. NSAID has common action of analgesic, antipyretic and anti-inflammatory action due to inhibition of prostaglandins.

There are two types of cyclooxygenase enzyme cyclooxygenase-1(COX-1) and cyclooxygenase-2 (COX-2) responsible for physiological and

pathological process respectively. COX-1 are present in platelets in blood and are responsible for tissue homeostasis and physiological process. COX-2 enzyme are present in the inflammatory cells and are activated by inflammatory cytokines Interleukin -1 (IL-1) and Tumour necrosis factor alpha (TNFα) and cause production of prostaglandins producing fever and pathological process.

The commonly used NSAID inhibit both the enzymes producing anti- inflammatory action. Recently selective COX-2 inhibitors have anti- inflammatory action without side effects produced due to COX 1 inhibition.

- **Metamizole** - Metamizole has been available worldwide since 1922 and it is an analgesic, antipyretic. It is a therapeutic agent from the group of pyrazoline derivatives. They are administered as a prodrug orally, rectally, intramuscularly or intravenously. The absorption is quick after oral administration and bioavailability is 85% and time till maximum plasma concentration (Tmax) of 1.2–2.0 h. After intravenous administration its analgesic effect begins within 30 minutes and last for approximately four hours. Metamizole is hydrolysed to active metabolites 4-methyl-amino-antipyrine (4-MAA) and aminoantipyrine (AA) and are excreted via the kidneys. The half-life is 2.5–3.5 h. In cases of severe toxicity or overdose it can be removed from the blood by hemodialysis.

The exact mechanism of its action is unknown and the findings from animal studies reveal that metamizole inhibits cyclooxygenase (COX) in peripheral tissues as well as the central nervous system. In the case of classic NSAIDs, COX activity is blocked by competing with arachidonic acid for the COX-binding site but in contrast, metamizole does not attach to this binding site but it inhibits the release from other binding places of free radicals, which are necessary to initiate COX-mediated arachidonic acid metabolism.

It has been revealed from a recently published meta-analysis that metamizole is an effective agent for alleviating post-operative pain. Indirect comparative studies had shown that 500 mg of metamizole was as effective as 400 mg of ibuprofen and more effective than 1000 mg of paracetamol. Contrary to NSAIDs, metamizole has low risk of gastrointestinal complications. Metamizole dilates the vascular smooth muscle and it can also reduce arterial pressure, especially when rapid intravenous administration is given. No adverse effects of metamizole on the cardiovascular system or kidneys were seen. Some of the contraindications for metamizole are allergies to metamizole and NSAIDs, severe arterial hypotension, hypovolaemia or shock, acute intermittent porphyria, glucose-6-phosphate dehydrogenase deficiency[40].

- **Paracetamol (acetaminophen)**- It is the most popular and most commonly used antipyretic and analgesic worldwide because of its low risk of adverse reactions and with proven analgesic efficacy. There are a

number of hypotheses regarding the central effects of paracetamol that could explain its analgesic efficacy. According to hypotheses regarding the central effects of paracetamol in analgesic activity, it inhibits the central activity of COX-2 and isoform of cyclooxygenase, COX-3. Warner and colleagues described two COX isoenzymes partial COX-1 (pCOX-1) and COX 3, predominantly seen within the human cerebral cortex and heart. It is believed that COX-3 is encoded by the same gene that encodes COX-2 but differs in its molecular characteristics. COX-3 is a variant of COX-2 , highly susceptible to paracetamol induced inhibition. Paracetamol also affect the antinociceptive serotonergic system thereby stimulating the activity of the descending serotonergic pathways (5-HT). The above hypothesis was supported by the finding the clinical trial that the combined use of paracetamol and antiemetic drugs like 5-HT_3 antagonists granisetron or tropisetron inhibited analgesic action of paracetamol.

Paracetamol is metabolised predominantly in the liver, and therefore caution should be taken in patients with active liver disease, long-term alcohol abusers and those with limited glutathione stores. Hepatotoxicity is caused by oxidised N-acetyl-p-benzoquinone imine (NAPQI) metabolite. It constitutes only 5% of paracetamol metabolites and is usually bound by glutathione. If the glutathione stores were depleted after overdose or were deficient, NAPQI binds liver proteins, causing necrosis of the central part of the hepatic lobules and it develops

over a period of 4 to 14 days. The cause of depleted glutathione levels include starvation, malnutrition, HIV infection and regular alcohol consumption. Paracetamol is an useful component of multimodal analgesia, which can be used in combinations with various opioids like codeine, tramadol and morphine[40,43].

- **Ibuprofen** – This is a propionic acid derivative . The oral absorption is rapid, 99% protein bound and the t1/2 is 2hrs. Excretion is rapid and complete and 90% is excreted as carboxylated and hydroxylated metabolite with or without glucuronide conjugation. It is a commonly used NSAID.
- **Diclofenac** - It is a phenylacetic acid derivative. It is a nonselective cycloxygenase inhibitors. It has analgesic, anti-inflammatory and antipyretic action. Oral absorption is rapid and complete with extensive first pass metabolism with bioavailabilty of 50%. 99% bound to plasma proteins with t1/2 of 1-2hrs. It is metabolized by CYP2C in the liver and excreted in urine and bile.It is useful for postoperative pain and can be used by parentral route, it can also be used for rheumatoid arthritis, osteoarthritis , tendonitis , bursitis , dysmenorrhoea.
- **Ketorolac** – It is a nonspecific cyclooxygenase inhibitor. It is a parenterally administered NSAID that provides analgesia by inhibiting prostaglandin synthesis. It is indicated for short term management of pain and useful for pain in immediate post - operative period .It does not cross the blood brain barrier it is a peripherally acting drug used

alternative to opioids for post- operative pain and it does not cause sedation or respiratory depression or nausea or vomiting. Dosage given is 60mg intramuscularly or 30mg intravenous loading dose with maintenance dose of 15-30mg every 6hours[44].

- **Lornoxicam**- It is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs), producing analgesic and antipyretic effects through the non-selective inhibition of cyclo-oxygenase-1 and -2. Besides its inhibitory effect on COX1 and COX-2 peripheral receptors, is also increases endogenous dinorphin and beta-endorphin levels promoting central analgesic and anti-inflammatory effects. Recently, lornoxicam has been introduced in Indian market in oral, intravenous and intramuscular formulations. Lornoxicam is completely absorbed after oral administration, reaching peak plasma concentrations of 280 mg/L within 2.5 hours after a 4 mg dose. After intramuscular injection maximum plasma concentrations are achieved after approximately 20-25 minutes. Lornoxicam is extensively metabolised in liver by cytochrome P4502DC9 to inactive metabolite 5'-hydroxy-lornoxicam. The mean elimination halflife is 3 to 4 hours[45].
- **Coxibs – COX-2 selective NSAID** - It has an action similar to conventional NSAIDs with the difference in selective inhibition of COX-2 . The advantages are it has less gastrointestinal side effects , do not precipitate bronchial asthma and has no antiplatelet action. The disadvantages are they increase the incidence of cardiovascular

thrombotic episodes and renal toxicity. Commonly used coxibs are celecoxib, rofecoxib, valdecoxib, parecoxib , lumiracoxib, etoricoxib. Parecoxib is the only coxib available as injection and effective analgesic for pre and postoperative period[43].

Adverse effects of the NSAIDs:

1. **Central nervous system:** Headaches, tinnitus, and dizziness.

2. **Cardiovascular:** Fluid retention, hypertension, edema, and rarely, myocardial infarction, and congestive heart failure.

3. **Gastrointestinal:** Abdominal pain, nausea, vomiting and rarely ulcers or bleeding.

4. **Hepatic:** Abnormal liver function tests and rarely liver failure

5. Hematologic: Rare thrombocytopenia, neutropenia, aplastic anemia.

6. **Pulmonary:** Asthma.

7. **Skin:** Rashes, pruritus.

8. **Renal:** Renal insufficiency, renal failure, hyperkalemia, and proteinuria[46].

ADVANCES IN PHARMACOLOGICAL MANAGEMENT OF ACUTE POSTOPERATIVE PAIN

New opioids and opioid formulations with unique pharmacodynamics profile, with analgesic effect and minimal adverse effects are being developed.

- **Tapentadol**- It is a centrally acting mu opioid receptor agonist and norepinephrine reuptake inhibitor approved for treatment of moderate to severe pain.
- **Patient controlled analgesia (PCA)** – It is safe and effective method of postoperative pain management. Intravenous opioids and pain controlled epidural analgesia with Opioids or local anasthetics are used in PCA.
- **Patient controlled regional anesthesia (PCRA)** – local anasthetics are administered in to surgical incision ,intra articular tissue ,or perineural site .
- **Patient controlled intranasal ketorolac tromethamine** – It was approved in 2010 for short term (5days) management of moderate to moderately severe pain in adults .
- **Patient controlled Fentanyl iontophoretic transdermal system (PCTA -fentanyl ITS)** It is an alternative to intravenous PCA. It is used for acute postoperative pain in adults . The advantage is lowers the risk of intravenous PCA related complications like mechanical pump errors, intravenous catheter infection and operating errors.
- **Patient controlled sublingual sufentanil system (PCSA)** – It is under development. It is designed in such a way to overcome the disadvantage of intravenous PCA like infections of indwelling intravenous catheter and human programming errors[38].
-

OTHER DRUGS USED FOR PAIN MANAGEMENT

- **Antiepileptics** – Gabapentin, Lamotrigine, Tiagabine, Phenytoin, Carbamazepine, Valproate, Oxcarbazepine, Clonazepam, Topiramate.
- **Antidepressants** – Amitriptyline, Nortriptyline, Desipramine, Citalopram Bupropion, Doxepine, Escitalopram Fluoxetine, Sertraline, Trazodone, venlafaxine.
- **Neuroleptics** – Fluphenazine , Haloperidol ,Chlorpromazine, Perphenazine.
- **Corticosteroids** – Hydrocortisone, Prednisone, Prednisolone, Methyl Prednisolone, Triamcinolone, Betamethasone , Dexamethasone .
- **Systemic local anasthetics** – Lidocaine, Procaine and Chloroprocaine most commonly used agents given as slow bolus or continuous infusion.
- **Alpha2 adrenergic agonists** – clonidine produce activation of descending inhibitory pathways in dorsal horn[47,48].

B. NON – PHARMACOLOGICAL MANAGEMENT OF PAIN

1. **Psychological interventions** – employed by psychiatrist and they include cognitive therapy ,behavioral therapy, relaxation technique and hypnosis.
2. **Physical therapy** – Heat and cold provides relief of pain by alleviating muscle spasm. Heat increases blood flow and cold vasoconstricts and reduce tissue edema. Superficial heating modalities are hotpacks, paraffin, hydrotherapy and deep heat application include ultrasound,

shortwave and microwave diathermy . For cold, cold packs, vapocoolant sprays and ice massage are used.

3. **Acupuncture** – It is a technique involves insertion of needles in to defined points. Studies suggest that acupuncture stimulates the release of endogenous opioids and its effects are antagonized by naloxone.
4. **Electrical stimulation** – it can stimulate the nervous system and can produce analgesia in patients with acute and chronic pain. Current is applied transcutaneously, epidurally or by electrodes implanted in to central nervous system.
    - **Transcutaneous electric nerve stimulation (TENS)** – produce analgesia by stimulating large afferent fibers. It has a role for patients with mild to moderate acute pain. In conventional TENS electrodes are placed in the same dermatome as the pain and stimulated by direct current periodically .A current of 10-30mA with pulse width of 50-80μs is applied at frequency of 80-100Hz. Patients refractory to conventional TENS respond to low frequency TENS and it is partly reversed by naloxone.
    - **Spinal cord stimulation (SCS)** – Also called as dorsal column stimulation as it was thought to produce analgesia by directly stimulating large Aβ fibers in the dorsal columns of spinal cord. The proposed mechanism is activation of descending modulating systems and inhibition of sympathetic out flow.

- **Intra cerebral stimulation** – Deep brain stimulation can be used for intractable cancer pain and also for neuropathic pain. Electrodes are implanted in to the periventricular and periaqueductal gray areas for nociceptive pain and for neuropathic pain placed in the specific sensory thalamic nuclei[47,48].

MASTOIDECTOMY

The primary goal in surgical management of chronic otitis media with cholesteatoma is creation of a dry safe ear through removal of disease and the alteration of anatomy to prevent the recurrence[49].

TYPES OF MASTOIDECTOMY

1. **Cortical mastoidectomy or simple mastoidectomy or schwatz mastoidectomy –** this was developed for the management of acute suppurative otitis media. It is a procedure that involves complete exenteration of all accessible mastoid air cells maintaining the integrity of post canal wall , middle ear structures and tympanic membrane inorder to have normal ear anatomically and physiologically.

- **Indications**
  a. Treatment of suppurative mastoiditis
  b. Masked mastoiditis
  c. Secretory otitis media in resistant cases

d. Chronic all discharging ear with central perforation
e. To expose mastoid segment of facial nerve
f. Exposure of mastoid region in canal wall up tympanoplasty
g. Saccus decompression surgery
h. Translabyrinthine operations
i. Retro labyrinthine approaches to vestibular nerve
j. Exposure of sigmoid sinus
k. Exposure of otic capsule for cochlear implant

- **Procedure** – After infiltration with 1% xylocaine with adrenaline post auricular incision from pinna to mastoid tip is made, superficial fascia ,muscles and periosteum are incised and separated. Mac Ewens triangle identified mastoid cortex and all matoid air cells are removed systematically under microscope with drill. Cavity edges saucerised and wound closed with interrupted sutures and drain. External auditory meatus is packed with cotton wick soaked in antibiotic ointment[50] .

  2.Canal wall up tympanoplasty (closed tympanoplasty) – It is an operation performed to remove disease from the mastoid antrum , air cell system, aditus-ad- antrum and the middle ear through facial recess (posterior tympanotomy) with preservation of an intact posterior bony external auditory canal without disturbing the middle ear contents.

- **Indications**

a. Cholesteatoma in children and patients with highly pneumatised mastoids.

b. Minor epitympanic, mesotympanic cholesteatoma
c. Cochlear implants
d. Facial nerve decompression

- **Procedure** – Simple matoidectomy is done, epitympanotomy and posterior tympanotomy done , middle ear is examined by elevating tympanomeatal flap. Cholesteatoma removed from the middle ear, attic and mastoid bone.

3.Canal wall down procedure (open cavity matoidectomy) - the objective is to clear the disease and to make the attic, aditus-ad-antrum , mastoid and external auditory meatus in to single cavity with wide meatoplasty ,preserving hearing and establishment if drainage .

- **Indications** :

a. Cholesteatoma in mastoid
b. Large epitympanic erosions
c. Recurrence after closed technique
d. Bilateral cholesteatoma
e. Only hearing ear
f. Large labyrinthine fistula
g. Severe sensory neural deafness
h. Benign tumours involving the middle ear
i. Malignant tumours of external auditory canal

- **Procedure** – simple mastoidectomy is the initial step . Bridge removed under magnification , anterior buttress is removed , facial ridge lowered

up to the floor of external auditory canal. Cavity is saucerised and wide meatoplaty done and wound closed in layers[50,51] .

5. **Modified radical mastoidectomty (Bondy)** – in this procedure the posterior canal wall is removed and the articulation between the ossicles are not touched.

- **Indications:**

a. Cholesteatoma
b. Post canal wall cannot be reconstructed
c. Nonfunctioning Eustachian tube
d. Poor patient compliance
e. Severe ontological or CNS complications

- **Procedure** – same procedure as open cavity technique and the ossicular chain is not disturbed, conchal cartilage used as a support to prevent recurrence of retraction of tympanic membrane[50,52,53,54].

5.Radical mastoidectomy – Objective is to clear the disease and to make middle ear , attic , aditus-ad-antrum , mastoid cavity and external auditory meatus in to one single cavity draining through the external auditory canal. All the ossicles in the middle ear and tympanic membrane are removed except foot plate of the stapes. Eustachian tube orifice is plugged with muscle or cortical bone.

- **Indications:**

a. Cholesteatoma with intracranial complications
b. Blind sac closure after glomus tumour excision[50].

6.Tympanoplasty – it is a procedure done to remove disease from middle ear , reconstruct hearing mechanism (ossiculoplasty) with or without repair of tympanic membrane. Usually tympanoplasty is combined with mastoidectomy.

- **Prerequisite for Tympanoplasty**

a. Adequate cochlear reserve must be present

b. Eustachian tube function should be normal

- **Types of tympanoplasty (Wullstein)**

Type 1- reconstruction of tympanic membrane, ossicular chain is intact and mobile.

Type 2- long process of incus is absent , remnant of incus is shaped and p0laced between handle of malleus and head of stapes

Type 3- malleus and incus are absent , graft is placwd over the ontact head of the stapes (columella effect / myringostapediopexy)

Type 4- round window (baffle effect) – All the ossicles are absent except mobile stapes foot plate . tympanic reconstruction is done by placing the graft over the promontory.

Type 5 – fenestration – All the ossicles are absent and foot plate of stapes is fixed an opening is made in the bony lateral semicircular canal.

Type 6 – sonoinversion – round window is exposed to sound waves and graft placed over the oval window[50,52,54].

ANESTHESIA FOR MASTOIDECTOMY

Local anesthesia is preferred by many surgeons for middle ear surgery . The advantages of local anesthesia are bleeding is less, presence of postoperative analgesia, mobilization of patient in short time, cost effective, reduced aspiration risk with normal cough reflex. Hearing can be tested during surgery and possibility of undergoing iatrogenic facial nerve weakness can also be evaluated.one hour before surgery preanasthetic medications like injection pentazocine, promethazine and atropine are given intramuscularly. Local anesthesia is given using 2% lignocaine with 1:10000 epinephrine for infiltration. Good patient selection is an important factor for the success of local anesthesia[55].

LORNOXICAM

Introduction - It belongs to Enolic acid oxicam group. Lornoxicam is a congener of tenoxicam, new nonsteroidal anti-inflammatory drug. It decreases prostaglandin synthesis by inhibiting cyclooxygenase. It has strong analgesic, antipyretic and anti-inflammatory effects. Its analgesic property is comparable to opioids. Lornoxicam has a short elimination half-life of 3–5 h when compared to other drugs that belong to oxicam group. Lornocicam also hass rapid onset of action when compared to other oxicam groups[56,57]

Chemical structure - Chemically it is a 4-hydroxycarboxamide [6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-5H-thieno(2,3-e)-[1,2]-thiazine-2-carboxamide-1,1- dioxide].

Mechanism of action - Lornoxicam (chlortenoxicam) inhibits prostaglandin (PG) synthesis via inhibition of cyclooxygenase both COX-1 and COX-2 and it does not inhibit 5-lipoxygenase. Lornoxicam also inhibits polymorphonuclear (PMN) leukocyte migration, inhibits the release of superoxide from human PMN-leukocytes, inhibits the release of platelet derived growth factor (PDGF) from human platelets and stimulates the synthesis of proteoglycans in cartilage in tissue culture.

Besides its inhibitory effect on the peripheral receptors of COX1 and COX-2 Lornoxicam also increases endogenous dinorphin and beta-endorphin levels promoting central analgesic and anti-inflammatory effects.

Intravenous lonoxicam (8mg) has been shown to be as effective as morphine (20mg), pethidine (50mg) and tramadol (50mg) in the treatment of postoperative pain.

Pharmacokinetic properties - Lornoxicam is completely absorbed after oral administration. After a 4mg oral dose peak plasma concentrations of 280 mg/L is reached within 2.5 hours. Studies have shown that the area under the serum drug concentration-time curve (AUC) is proportional following lornoxicam doses between 2 to 6mg given twice daily for 2 weeks in healthy young volunteers. Cmax and AUC of lornoxicam indicated drug accumulation

upon repeated administration. Intra-gastric food delays and reduces the absorption of lornoxicam.

After intramuscular injection of lornoxicam maximum plasma concentrations are achieved approximately after 20-25 minutes. The bioavailability after intramuscular injection is 97 percent. The plasma protein binding is 99 per cent and the apparent volume of distribution of lornoxicam is low (0.3L/Kg). It is extensively metabolised in liver by cytochrome P4502DC9 in to inactive metabolite 5'-hydroxy-lornoxicam. It has been found that approximately 51 percent drug is excreted in faeces and 42 percent via kidneys as inactive substance. The mean elimination half life of lornoxicam is 3 to 4 hours. The drug has been found to be safe in elderly patients and in patients with impaired renal function and hepatic functions[56,57,58].

Therapeutic uses

a. <u>Analgesia</u> - It produce dose related analgesia in acute and chronic pain .It is useful in the treatment of postoperative pain and other acute traumatic painful condition like fractures. It is also useful in acute sciatica, lumbosciatica and chronic low back pain. It can decrease the opioid requirement when used as an adjunctive analgesic in patients with cancer pain. It can decrease the headache episodes in the migraine patients.

b. <u>Anti inflammation</u> – it improves pain and functional disability in osteoarthritis, ankylosing spondylitis and rheumatoid arthritis.

c. <u>Herpetic stromal keratitis</u> – Experimental study in mice demonstrated the down regulation of NF-kappa B activation produced protective effect against herpetic stromal keratitis.

d. <u>others</u> – used in rheumatoid arthritis for inhibition of release of superoxide from polymorphs and inhibition of release of platelet derived growth factor from platelets[56].

Drug Interactions - Lornoxicam metabolism is inhibited by clonazepam and diazepam and it does not interact with ranitidine and antacids. Co-administration of lornoxicam and anticoagulants or platelet aggregation inhibitors may prolong the bleeding time. It also increases the hypoglycemic effect of sulphonylureas and decrease the efficacy of diuretics and ACE inhibitors. Cimetidine co-administration inhibits elimination of lornoxicam with significant increase in steady state Cmax and reduction in plasma clearance. It decreases plasma digoxin clearance and increases methotrexate concentration[57].

Dosage and administration - The most common dosages of lornoxicam used in clinical trials are 4 mg twice or 3 times daily or 8 mg twice daily (orally) for management of arthritic conditions, low back pain and ankylosing spondylitis. For the management of postoperative pain single or repeated doses of 4 or 8 mg (orally or intravenously) lornoxicam is used. Quick-release formulation and injectable formulations of lornoxicam is available and it is also available in powder form as vial of 8mg for intramuscular and intravenous use. The powder

is dissolved in 2ml water for injection immediately prior to use. As an intramuscular injection lornoxicam must be administrated in more than 5 seconds[56,57].

Tolerablility - Lornoxicam has a characteristic tolerability profile of NSAIDs, with gastrointestinal disturbances (pain, dyspepsia, nausea, vomiting) being the most prominent events. The tolerability of oral lornoxicam appeared to be similar to that of diclofenac and better than that of indomethacin in patients with arthritic conditions or chronic low back pain in comparative clinical trials. Lornoxicam is better tolerated than parenteral opioid analgesics in patients with postoperative pain[59].

CLINICAL STUDIES RELATED TO LORNOXICAM

Many studies show that lornoxicam is effective and well tolerated in the treatment of many acute painful conditions like acute sciatica/lumbosciatica, acute low back pain and acute post-operative pain following gynaecological, orthopaedic or other surgeries. Lornoxicam has been used in several clinical trials for postoperative pain relief after various surgical procedures.

Arslan et al studied the postoperative analgesic effect of lornoxicam after thyroidectomy in a placebo controlled randomized trial by using a dose of 8mg intravenous at the end of surgery followed by 8mg twice a day for 24 hours postoperatively. Authors concluded that pain scores and the incidence of nausea and vomiting decreased with the use of lornoxicam.

Lornoxicam is more than a decade old NSAID and it has been recently introduced in India. A small number of preliminary placebo-controlled and comparative clinical studies shows that lornoxicam provides effective analgesia following surgery[45].

Lorenz et al reported that intravenously administered lornoxicam suppressed pain induced brain activation in all regions except hippocampus which was shown in a Functional magnetic resonance imaging (FMRI).

Yakhnoet et al studied the variation in formulations and found that lornoxicam administered as quick formulation was non inferior to equivalent formulation of diclofenac in pain relief [59].

Sener et al in a prospective placebo controlled, double blind, randomized study compared the efficacy of lornoxicam with diclofenac , ketoprofen and dipyrone for acute postoperative pain management in post septoplasty patients. Lornoxi8cam 8mg and diclofenac 75mg twice daily, ketoprofen 100mg twice daily, dipyrone 1gm thrice daily and placebo twice daily showed no significant difference between four groups[60].

Sapolya et al studied the analgesic effects of lornoxicam after total abdominal hysterectomy in a randomised double blind study where tramadol is used as patient controlled analgesia. They concluded that a single oral dose of lornoxicam given preoperatively enhanced the analgesic effect of tramadol thereby decreasing the consumption of tramadol and side effects and shortened the length of hospitalization[61]

Daglar et al conducted a study to compare the efficacy and tolerability of lornoxicam and diclofenac in pain management after coronary artery bypass grafting (CABG) . The study concluded that the efficacy of lornoxicam and diclofenac were similar in postoperative pain management and both the study drugs were well tolerated[5].

In a study done by Mohamed Daabiss et al in analgesia in day care ENT surgery the efficacy of lornoxicam in patient receiving intravenous lornoxicam 8mg or 16 mg before induction with fentanyl was studied. The study revealed that lornoxicam 16mg is comparable to fentanyl as an intraoperative intravenous analgesia and it was found that lornoxicam was more effective than fentanyl in preventing early postoperative pain patients undergoing minor to moderate day care ENT surgical procedure[6].

CLINICAL STUDIES RELATED TO DICLOFENAC:

Anirban et al in a clinical study on post‑operative analgesia in patients undergoing lower abdominal gynecological surgeries ,between injection Diclofenac 75mg intramuscularly and injection Paracetamol 1gm intravenously 8th hourly for 24 hours postoperative period showed that injection Diclofenac given intramuscularly was superior to intravenous Paracetamol in terms of rescue analgesic requirement. The study also showed that the combination of intramuscular Diclofenac and intravenous Paracetamol had no added advantage over Diclofenac intramuscularly given alone[62].

Ashima Taneja et al in a comparative study on the effect of Paracetamol, Diclofenac and their combination in post-operative relief of cesarean section concluded that balanced analgesia with combination of Diclofenac and Paracetamol considered as the preferred method for postoperative pain following cesarean section[63].

Cengiz Kara et al in a clinical study on the analgesic efficacy and safety of Non steroidal anti inflammatory drugs administered as intramuscular diclofenac in comparison with intravenous paracetamol after transurethral resection of prostate (TURP) showed that single dose of diclofenac alone is more effective for pain relief than single infusion of paracetamol[64].

With the above extensive literature review there is lack of studies on the comparison of lornoxicam with diclofenac in the management of postoperative pain, so this study was designed to compare the efficacy and safety of injection Lornoxicam given twice daily with twice daily dose of injection Diclofenac for 3 days in the management of postoperative pain following Mastoidectomy surgery.

AIM OF THE STUDY

Aim of the present study is to evaluate the efficacy and safety of the analgesic, Lornoxicam when compared to Diclofenac in the management of postoperative pain following mastoidectomy surgery.

METHODOLOGY

MATERIALS AND METHODS

STUDY TYPE:

Interventional clinical study.

STUDY DESIGN:

Prospective, single blind, randomized, parallel group study.

STUDY PERIOD:

April 2014 – May 2015

STUDY CENTRE:

It is a single centered study conducted in the patients undergoing Mastoidectomy Surgery in the Department of Ear Nose Throat, Tirunelveli Medical College Hospital, Tirunelveli.

STUDY DURATION: Three days for each individual patient

SAMPLE SIZE: Total of 80 patients (40 patients in Lornoxicam group and 40 patients in diclofenac group)

INCLUSION CRITERIA:

- Patients of both sex.
- Patients aged >18 years and < 70 years.
- Patients undergoing Mastoidectomy surgery

EXCLUSION CRITERIA: Patients with the following criteria are excluded from the study.

- Patients Hypersensitive to drugs
- Patients with Bronchial asthma, Hypertension
- Patients with Diabetes mellitus, Peptic ulcer disease and Seizure.
- Patients with the history of Substance abuse.
- Patients with Liver and /or Kidney disease.
- Patients receiving NSAIDS, Sedatives and Hypnotics or Psychotropic drugs.
- Patients with the history of Bleeding diathesis
- Pregnant and lactating mother.

WITHDRAWAL CRITERIA:

- Noncompliance with protocol
- Protocol deviation
- Request for withdrawal by the patients
- Adverse effects (decision about with drawl from the study was made either by patient or investigator)

ETHICAL CONSIDERATION:

Approval from the Institutional Ethical committee was obtained. Written informed consent was obtained in local vernacular language from every patient before enrollment.

SCHEDULE OF STUDY:

Screening and Recruitment:

The subjects were enrolled based on inclusion criteria after screening. During enrollment clinical assessment and the following base line investigations were done.

- Complete blood count
- Bleeding time and clotting time
- Random blood sugar
- Blood urea
- Serum creatinine
- Liver function tests

Randomisation :

After enrollment subjects were randomized into two groups (group A and group B) with the help of computer generated random table.

Treatment Protocol :

The patients in this study after randomisation received postoperative analgesics as follows :

Group A: Injection Lornoxicam 8mg given intramuscularly twice daily for 3days.

Group B: Injection Diclofenac 75mg given intramuscularly twice daily for 3days.

In both the groups first dose of the analgesic was given to all the study patients immediately after the skin closure and the rest of the doses were given every twelve hours for three days.

Pain assessment

Visual analogue scale (VAS) and Wong Baker FACES pain rating scale (WBS) was used to measure the pain level. VAS is a 10cm horizontal line graduated scale with 0 to 10, 0 is no pain and 10 is worst pain. Patients were asked to assess their pain on their own and mark on the VAS. Interpretation of scoring is 0 to 0.4cm is no pain, 0.5 to 4.4cm is mild pain, 4.5 to 7.4cm is moderate pain and 7.5 to 10 cm is severe pain[7] . The pain assessment with WBS was done with six facial expressions suggesting various pain intensities.

The first pain assessment was done 1hour after the patient received the first dose of the drug. Following which pain assessments were done after 3hours, 6hours, 12hours, 24 hours, 48 hours and 72 hours.

Rescue medication:

Any medication used to treat pain after initiation of analgesics is rescue medication. Injection Paracetamol was used as the rescue drug in this study. After giving the study drug, when the patient complained of severe pain and if the VAS score was more than 7 and WBS more than 8, injection

Paracetamol 300mg was given intramuscularly to the patients. Number of patients requiring rescue drug and time when rescue drug was needed by the patients were noted in each study group.

Follow up:

Follow up was done on the day of surgery 1hour, 3 hour, 6 hour and 12 hour following the first dose of anti-inflammatory drug. On the first postoperative day, approximately 24 hours after the administration of first dose follow up was done. Similarly on the second and third postoperative day, approximately 48 hours and 72 hours respectively the follow up was done.

During the follow up, VAS and WBS scoring was done and physical examination including vital signs like pulse rate, blood pressure and temperature were noted. Patients were also enquired about adverse events and use of rescue medication and time to use rescue medication through three postoperative days.

EFFICACY PARAMETERS

Primary endpoints: Analysis of postoperative pain using

- 10cm visual analogue scale (VAS) pain score
- Wong Baker FACES pain rating scale (WBS) pain score.

Secondary endpoints:

- The usage of rescue medication by the patients
- Time to use the rescue drug by the patients in each study group.

SAFETY ASSESSMENTS:

Any adverse events reported by the subject or noted by the clinician during the each follow-up visit were recorded. In case of treatment emergent adverse event, the subject could be withdrawn if continuation of the drug was considered harmful. Any adverse event was considered as serious if it was fatal, life threatening, disabling or if it prolonged the hospitalization of the subject.

LABORATORY ASSESSMENTS:

Blood samples were obtained preoperatively and on the third post-operative day**.** Parameters assessed were the hemodynamic properties like hemoglobin, total blood count, differential count, erythrocyte sedimentation rate, platelet count, bleeding time, clotting time and random blood sugar. Other parameters measured are liver function test like direct, indirect and total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase and even the albumin, globulin and total proteins were measured. Renal function test like blood urea and serum creatinine were also measured.

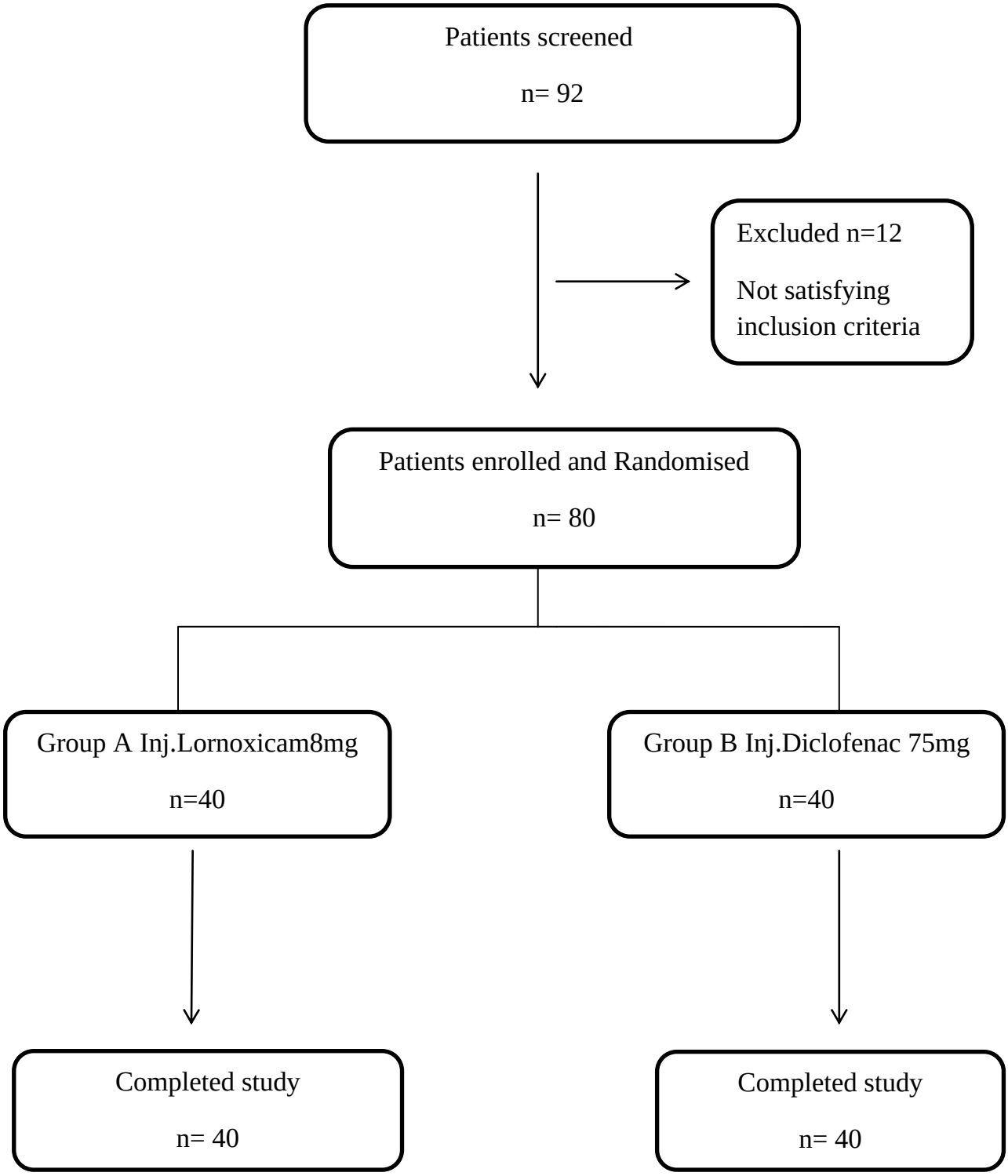
STATISTICAL ANALYSIS:

Statistical analysis was performed with the help of statistical package SPSS (Statistical Package for the Social Sciences) version 11 .

- Baseline characteristics of both the groups were tabulated by descriptive statistics (mean , standard deviation) and frequency table. They were matched by unpaired student 't' test and Pearson's chi - square test .
- Between the two groups the analysis of primary parameters was done using student unpaired ‘t’ test at 1 hour, 3 hour, 6 hour, 12hour, 24hour, 48 and 72 hour of the study.
- The time to use rescue medication was expressed in mean and standard deviation and the proportion of patients required rescue medication and their association between two groups were done using Pearson chi square.
- The adverse effects were expressed in percentage and the association between two groups were done using Pearson chi square.

To compare two groups, p values less than 0.05 ($p<0.05$) was considered as significant in two tailed condition.

PATIENT DISPOSITION: CONSORT DIAGRAM



RESULTS

For a period of one year April 2014 to May 2015, 92 patients (44 male patients and 48 female patients) were assessed for eligibility based on the inclusion and exclusion criteria. 80 patients were enrolled for the study and they were randomised in to group A and group B .Group A (n = 40) received injection Lornoxicam 8mg and group B (n = 40) received injection Diclofenac 75mg. Out of these 80 patients 40 patients in group A and 40 patients in group B completed the study.

TABLE -1

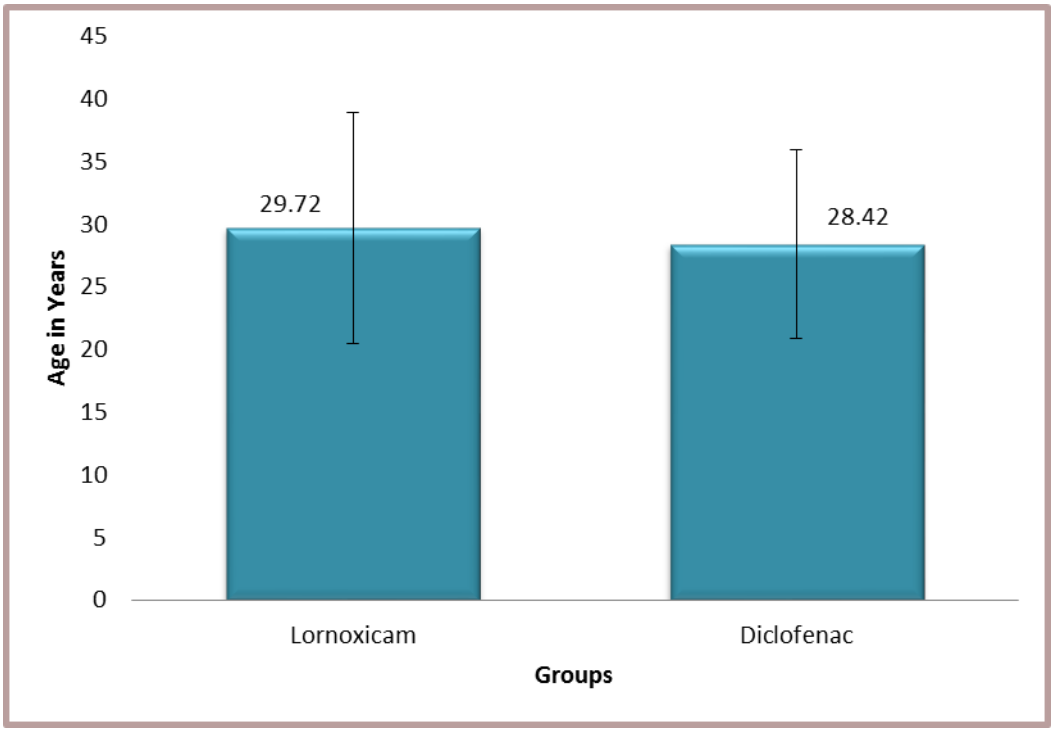
BASELINE CHARACTERISTICS

BASELINE PARAMETERS		**INJ.LORNOXICAM GROUP A n = 40**	**INJ.DICLOFENAC GROUP B n=40**	**P VALUE**
Age yrs (mean/SD)		29.72 ± 9.21	28.42 ± 7.54	0.492
Gender n (%)	Male	19 (47.5%)	19 (47.5%)	
	Female	21 (52.5%)	21 (52.5%)	
Weight (Kgs) (mean/SD)		65.52 ± 5.12	64.52 ± 5.79	0.416
Duration of Surgery (min) (mean/SD)		91.12 ± 12.88	88.50 ± 10.07	0.313
Hb (%)(mean/SD)		13.56 ± 1.47	13.6 ± 1.35	0.9
WBC (cells/cumm) (mean/SD)		8490 ± 1274.16	8112.5 ± 1294	0.192
Platelet count (lakhs/cumm) (mean/SD)		2.93 ± 0.65	2.77 ± 0.63	0.26
Blood sugar (gms%) (mean/SD)		92.07 ± 9.09	93.45 ± 9.72	0.516

Table 1 shows the baseline characteristics of both the groups. Baseline characteristics were similar in both the groups ($p>0.05$).

FIGURE 3

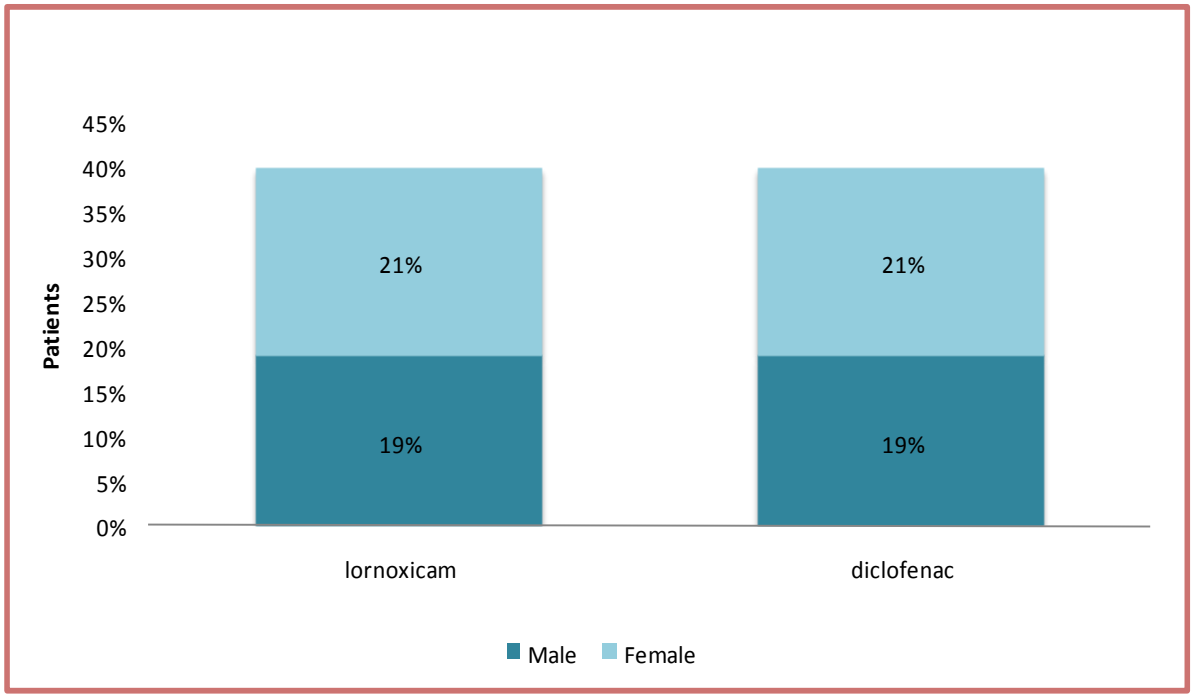
MEAN AGE OF TWO GROUPS



- Figure 3 shows the pictorial diagram of mean age distribution between two groups.
- In lornoxicam group the mean age was 28.42 years and the mean age in diclofenac group was 29.72 years
- Both the groups were comparable with no statistically significant difference.

FIGURE 4

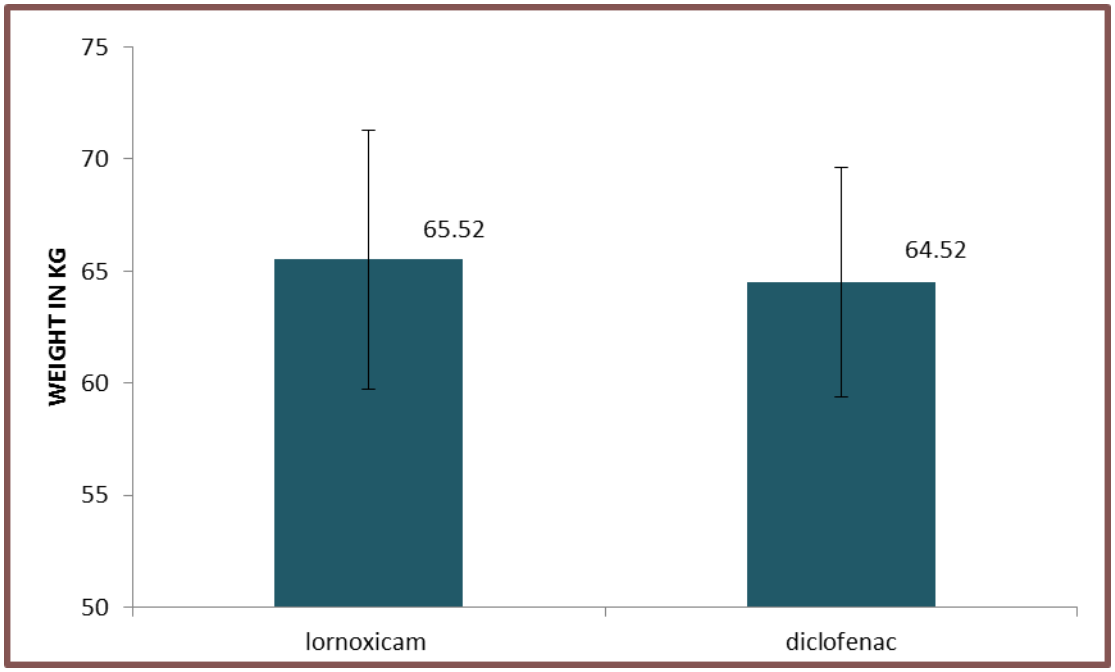
SEX DISTRIBUTION OF TWO GROUPS



- Figure 4 shows the diagrammatic representation of the sex distribution of two groups in the study.
- 19% were males in both the groups and 21% were females.
- Both the groups were comparable with no significant difference between two groups.

FIGURE 5

MEAN WEIGHT OF TWO GROUPS



- Figure 5 Shows the pictorial representation of the mean weight of the two groups.
- The mean weight in lornoxicam group was 65.52 kg and in diclofenac group 64.52 kg.
- Both the groups were comparable with no significant difference between the two groups.

PRIMARY EFFICACY PARAMETERS

TABLE – 2

VAS PAIN RESPONSE RATES

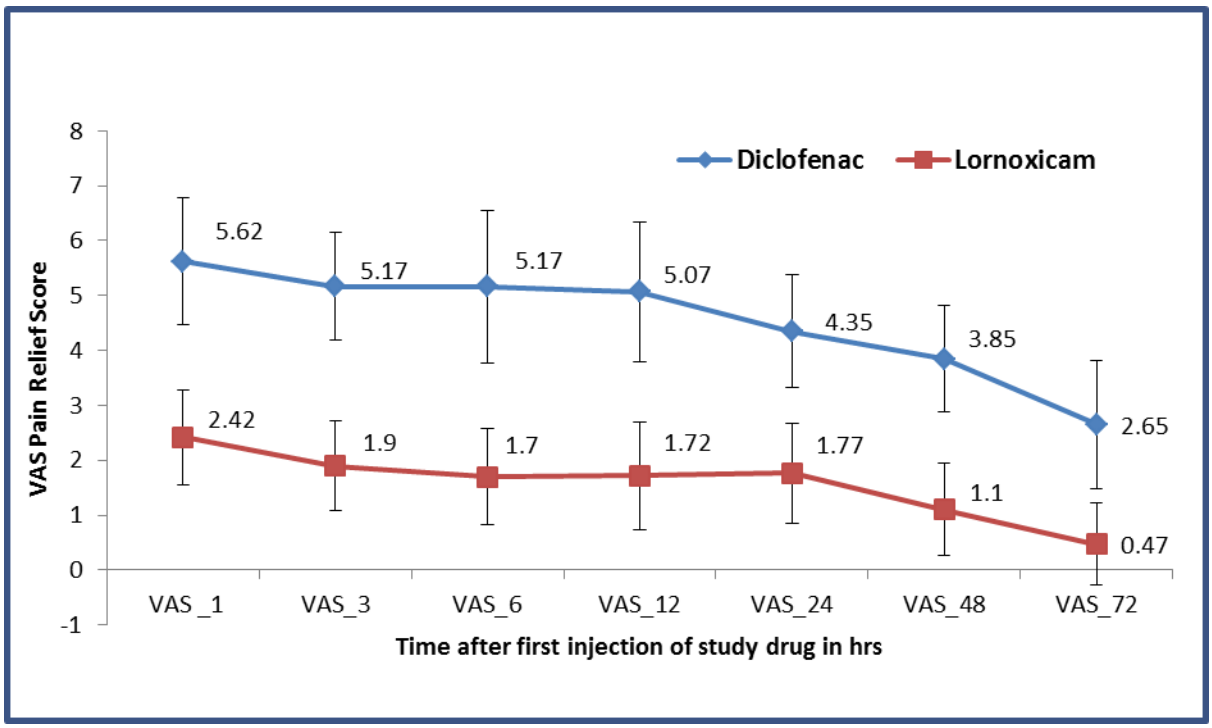
VAS	INJ LORNOXICAM GROUP A	INJ DICLOFENAC GROUP B	P VALUE
	MEAN ± SD	MEAN ± SD	
VAS_1	2.42 ± 0.87	5.62 ± 1.16	< 0.0001*
VAS_3	1.9 ± 0.81	5.17 ± 0.98	< 0.0001*
VAS_6	1.7 ± 0.88	5.17 ± 1.39	< 0.0001*
VAS_12	1.72 ± 0.98	5.07 ± 1.28	< 0.0001*
VAS_24	1.77 ± 0.91	4.35 ± 1.02	< 0.0001*
VAS_48	1.1 ± 0.84	3.85 ± 0.97	< 0.0001*
VAS_72	0.47 ± 0.75	2.65 ± 1.16	< 0.0001*

*** p value <0.05, statistically significant**

- Table 2 shows the visual analogue scale score comparison of efficacy of Lornoxicam and Diclofenac.
- Lornoxicam produced significant reduction in the postoperative pain than diclofenac at 1hr, 3hr, 6hr, 12hr, 24hr, 48hr, 72hrs. ($p<0.0001$).

FIGURE –6

MEAN (SD) VAS PAIN RELIEF SCORES IN THE STUDY POPULATION



- Figure 6 shows the graphical representation of VAS score of Lornoxicam and Diclofenac group.
- Pain relief was assessed using visual analog scale (0 - no pain to 10- worst pain imaginable)
- Both the groups showed reduction in pain throughout the study and the pain reduction was more with lornoxicam group.

PRIMARY EFFICACY PARAMETERS

TABLE – 3

WBS PAIN RESPONSE RATES

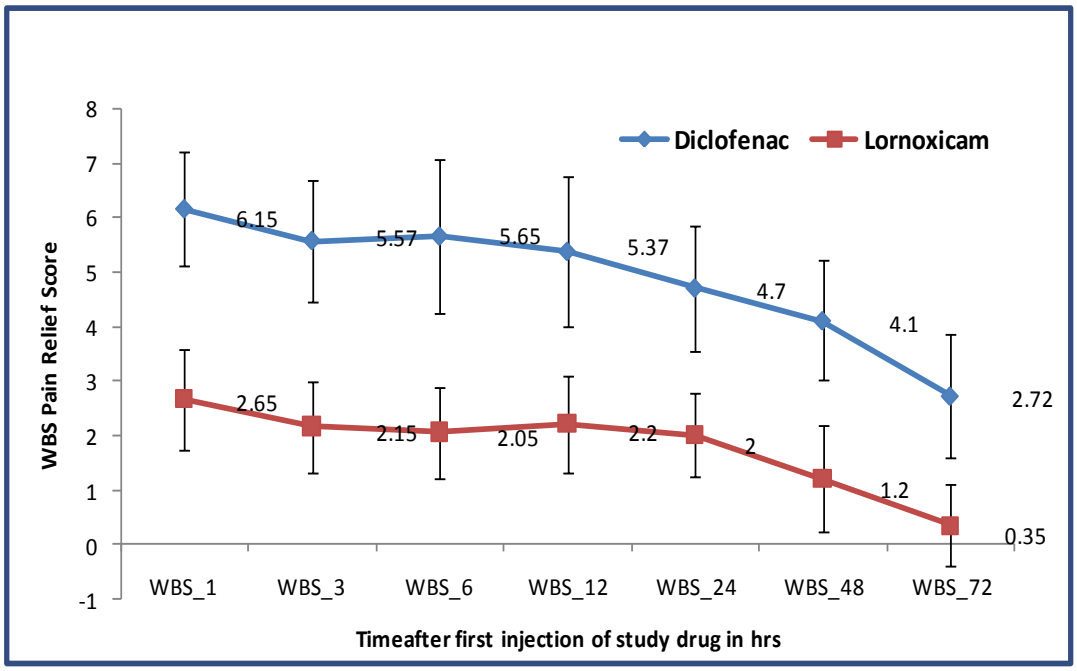
VAS	INJ LORNOXICAM GROUP A	INJ DICLOFENAC GROUP B	P VALUE
	MEAN ± SD	MEAN ± SD	
VAS_1	2.42 ± 0.87	5.62 ± 1.16	< 0.0001*
VAS_3	1.9 ± 0.81	5.17 ± 0.98	< 0.0001*
VAS_6	1.7 ± 0.88	5.17 ± 1.39	< 0.0001*
VAS_12	1.72 ± 0.98	5.07 ± 1.28	< 0.0001*
VAS_24	1.77 ± 0.91	4.35 ± 1.02	< 0.0001*
VAS_48	1.1 ± 0.84	3.85 ± 0.97	< 0.0001*
VAS_72	0.47 ± 0.75	2.65 ± 1.16	< 0.0001*

*** p value <0.05, statistically significant**

- Table 3 shows the Wong Bakers pain scale score comparison of efficacy of Lornoxicam and Diclofenac.
- Lornoxicam produced significant reduction in the postoperative pain than diclofenac at 1hr, 3hr, 6hr, 12hr, 24hr, 48hr, 72hrs. ($p<0.0001$)

FIGURE -7

MEAN (SD) WBS PAIN RELIEF SCORES IN THE STUDY POPULATION



- Figure 7 shows the graphical representation of WBS pain score of Lornoxicam and Diclofenac group.
- During the first 12 hour period maximum reduction of pain was seen in 6th hour in lornoxicam group and 12th hour of diclofenac group.
- The reduction in pain score is more in lornoxicam group than diclofenac group throughout the study.

SECONDARY PARAMETERS

TABLE- 4

PROPORTION OF PATIENTS REQUIRED RESCUE MEDICATION

GROUPS	RESCUE MEDICATION REQUIRED		P VALUE
	YES	NO	
GROUP A	3(7.5%)	37(92.5%)	0.019*
GROUP B	11(27.5%)	29(72.5%)	

*** p value <0.05, statistically significant**

- Table 4 shows the proportion of patients who required rescue medication in both the study groups.
- In study group A (lornoxicam) 3 patients required rescue medication and in study group B (diclofenac) 11 patients required rescue medication.
- More number of patients in diclofenac group required rescue medication than the lornoxicam group which was statistically significant.

SECONDARY PARAMETERS

TABLE - 5

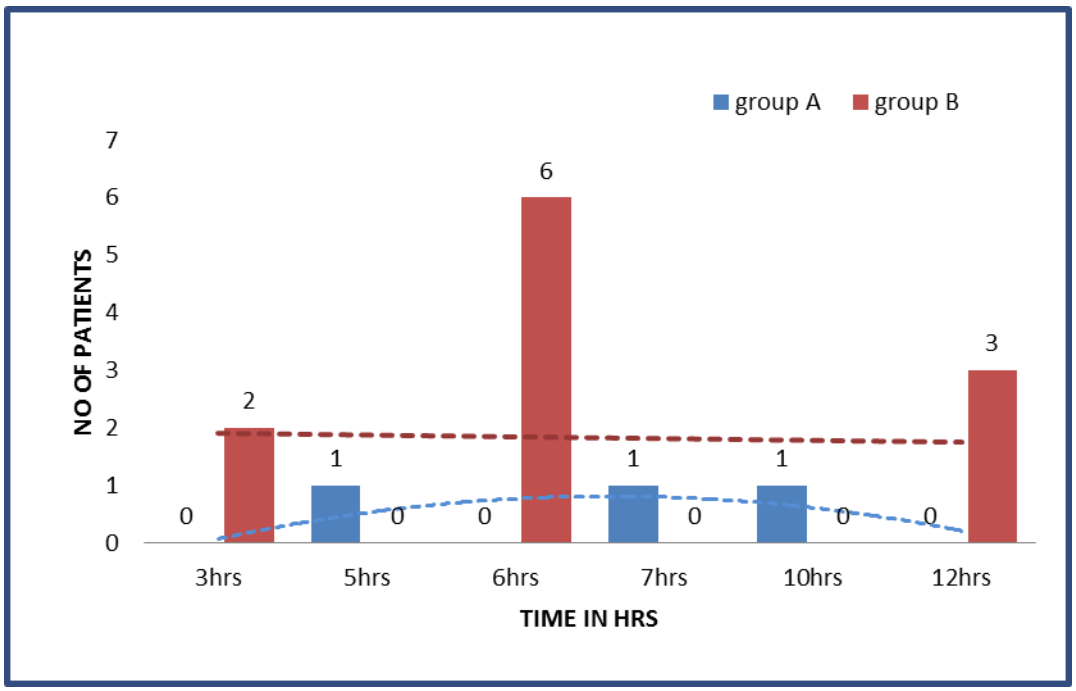
TIME TO USE RESCUE MEDICATION

GROUPS	NUMBER OF PATIENTS	TIME TO USE RESCUE MEDICATION (hrs)
		MEAN ± S.D
Group A	3(7.5%)	7.33 ± 2.51
Group B	11(27.5%)	7.09 ± 3.36

- Table 5 shows the mean time to use rescue medication
- In lornoxicam group the mean time to use rescue drug was 7.33 ± 2.21 hours after the first dose
- In diclofenac group the mean time required to use rescue medication was 7.09 ± 3.36

FIGURE - 8

TIME TO USE RESCUE MEDICATION OF 2 GROUPS



- Figure 8 shows the pictorial representation of number of patients required rescue drugs and time to use the rescue drug.
- The above graph shows that in diclofenac group, 2 patients required rescue medication at 3 hours after first dose, 6 patients required rescue medication 6 hours following the first dose of the drug and 2 patients at 12 hours following the first dose.
- In lornoxicam group only one patient required rescue medication at 5hours, 6hours and 10 hours.

- Based on the comparison of trend line between the two groups, more number of patients utilised the rescue drugs in the diclofenac group between 3rd to 12th hour following first dose than lornoxicam group.
- The maximum number of patients who required rescue medication was in diclofenac group in the 6th hour following the first dose of analgesic.

TABLE – 6

RENAL AND LIVER FUNCTION PARAMETERS OF LORNOICAM GROUP

PARAMETERS	PREOPERATIVE Mean ± SD	POSTOPERATIVE Mean ± SD	PVALUE
Serum Creatinine mg/dl	0.76 ± 0.07	0.77 ± 0.08	0.279
Blood Urea mg/dl	25.02 ± 2.06	25 ± 2.14	0.959
ALT U/L	28.67 ± 2.67	29.35 ± 2.55	0.202
AST U/L	22.60 ± 2.12	22.47 ± 2.89	0.835
ALKP U/L	49.25 ± 1.80	49.90 ± 1.82	0.128
Total BilirubinU/L	0.71 ± 0.6	0.72 ± 0.6	0.881
Total ProteinU/L	6.86 ± 0.45	6.84 ± 0.34	0.757

- Table 6 shows the Renal and Liver function test of lornoxicam group
- The renal function test like blood urea and serum creatinine in study patients of lornoxicam group showed no significant difference between the preoperative and postoperative values.

TABLE – 7

RENAL AND LIVER FUNCTION PARAMETERS OF DICLOFENAC GROUP

PARAMETERS	PREOPERATIVE Mean ± SD	POSTOPERATIVE Mean ± SD	PVALUE
Serum Creatinine mg/dl	0.77 ± 0.10	0.78 ± 0.10	0.706
Blood Urea mg/dl	24.5 ± 2.17	24.67 ± 1.71	0.594
ALT U/L	28.62 ± 2.24	28.52 ± 2.33	0.851
AST U/L	22.17 ± 2.53	21.47 ± 2.57	0.248
ALKP U/L	50.47 ± 1.50	50.15 ± 4.09	0.668
Total BilirubinU/L	0.73 ± 0.21	0.77 ± 0.29	0.244
Total ProteinU/L	7.02 ± 0.26	7.05 ± 0.19	0.573

- Table 7 shows the Renal and Liver function parameters of diclofenac group
- There was no signinificant difference between the preoperative and postoperative values of renal and liver function test in diclofenac group of study population.

ADVERSE EFFECTS

All the patients in both the groups completed the study. Both drugs were well tolerated. No serious adverse events were noted in two groups. The common adverse effects noted are tabulated below.

TABLE - 8

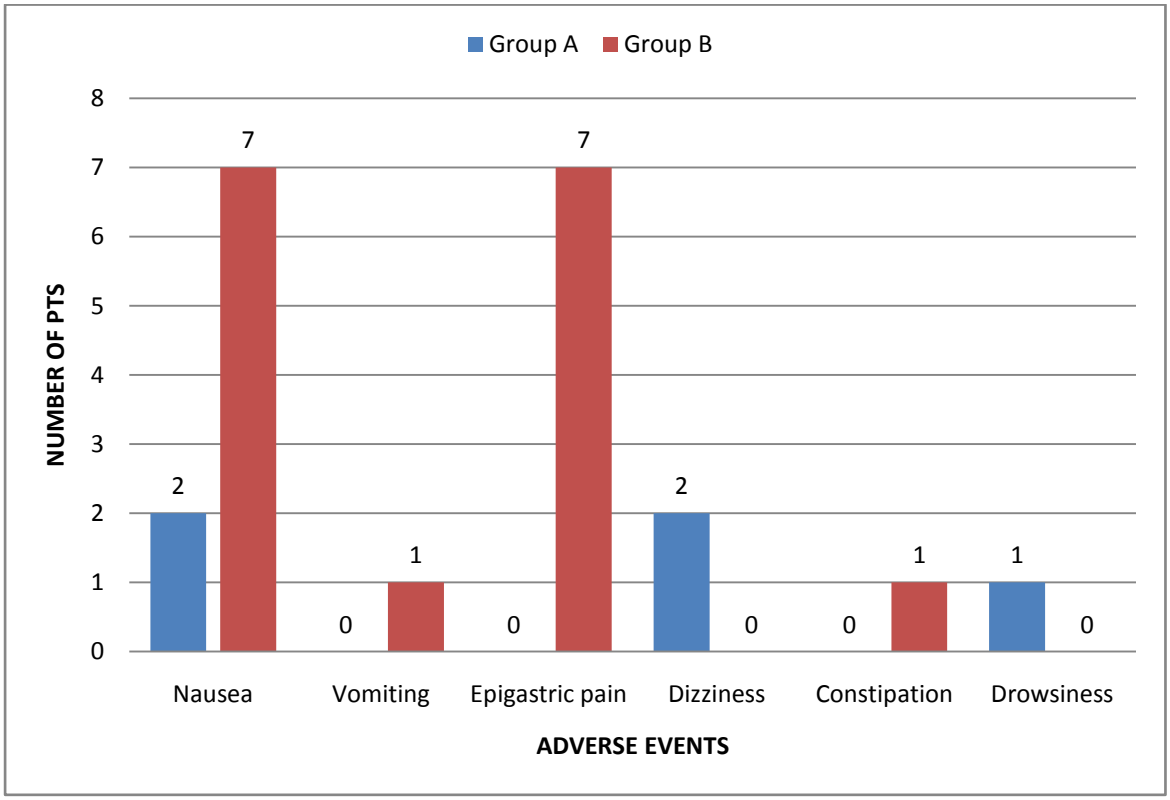
NUMBER OF PATIENTS WITH SPECIFIC ADVERSE REACTION

ADR	GROUP A n / (%)	GROUP B n / (%)
Nausea	2 (5)	7 (17.5)
Vomiting	-	1 (2.5)
Epigastric pain	-	7 (17.5)
Dizziness	2 (5)	-
Constipation	-	1 (2.5)
Drowsiness	1 (2.5)	-

- Table 8 shows that in diclofenac group, 7 (17.5%) patients developed nausea and epigastric pain, 1 (2.5%) patient developed vomiting and constipation .
- In lornoxicam group 2 (5%) patients developed nausea and dizziness and 1 (2.5%) developed drowsiness.

FIGURE – 9

PATIENTS WITH COMMON ADVERSE REACTION IN TWO GROUPS



- Figure 9 shows the adverse reaction that occurred in two groups during the study period.
- In diclofenac group the most common adverse reaction developed was nausea and epigastric pain.
- In lornoxicam group the most common adverse reactions developed was nausea and dizziness

DISCUSSION

Effective postoperative pain management is an important concern for anesthesiologist and surgeon[65]. Approximately 80% of patients undergoing surgical procedures experience mild to severe post-operative pain, despite the major improvements in the understanding of post-operative pain pathology[7].

Mastoidectomy is one of the common surgical procedures done under local anasthesia in the department of otorhinolaryngology. The most frequently used NSAID in the management of postoperative pain is diclofenac and they are associated with increased incidence of adverse effects like abdominal pain, dyspepsia, heartburn, gastrointestinal ulcer and diarrhea[66]. Lonoxicam is a NSAID with high therapeutic potency of oxicams with reduced gastrointestinal toxicity when compared to other group of its class[1]. So the present study was carried out to compare diclofenac with lornoxicam. When oral administration is not possible or rapid analgesia is needed following surgery parentral route of administration is the route of choice[67]. Therefore the preferred route of administration of analgesic in this study was intramuscular route.

Lornoxicam has been used successfully in prevention and treatment of post-operative pain and it has been shown to be as effective as morphine, meperidine and tramadol[6]. Lornoxicam as well as diclofenac have been used for post-operative pain relief in various surgical procedures and these drugs are

used individually or in combination with other drugs using different rescue drug in different studies[7].

In our study the mean age of the patients in lornoxicam group was 29.72 ± 9.21 years and in the diclofenac group it was 28.42 ± 7.54 years with no significant difference between the two groups. The mean age was similar to another study conducted by Geetha Bhandari et al[68]. The sex distribution in the present study was equally distributed between both the groups with male patients of 19 (47.5%) and female patients of 21 (52.5%) in group A and group B. This showed that during our study period female patients who underwent mastoidectomy surgery were more than males. This was similar to another study conducted by Dae Wook et al on mastoidectomy patients[69]. The mean weight of patients in both the groups were 65.52 ± 5.12 kg and 64.52 ± 5.79 in lornoxicam and diclofenac respectively with no significant difference between the two study groups. The mean weight was similar to study conducted by Dae Wook et al[69].

In the present study administration of lornoxicam for acute postoperative pain following mastoidectomy surgery resulted in statistically significant (p value <0.0001, table2 and 3) decrease in VAS score and WBS score throughout the study when compared to patients who received diclofenac. The maximum reduction of pain intensity in the first 12 hour period was 6 hour following the first dose of lornoxicam and 12 hours following first dose of diclofenac. This showed the earlier onset of action of the drug lornoxicam. This is comparable to study done by sudip et al in comparative study of efficacy and

safety of lornoxicam versus tramadol as analgesics after surgery on head and neck showed that lornoxicam had early onset action[1]. VAS and WBS has been used to evaluate the efficacy of pain management of acute postoperative pain because of its defining pain intensity and reliability[67]. The present study is similar to study done by Galani Varsha et al, in which lornoxicam and diclofenac were compared in patients with acute postoperative pain after spinal surgery the result showed significantly greater analgesic effect by lornoxicam at 30 minutes and 300 minutes when compared to diclofenac[7]. Similar to our study there are few studies available comparing the efficacy and safety of lornoxicam and diclofenac, Vishalkumar et al studied the efficacy and safety of lornoxicam and diclofenac in osteoarthritis knee patients the results showed that lornoxicam significantly relieved pain more than diclofenac[59]. Sushila godara et al conducted a study by comparing lornoxicam and diclofenac in the management of acute renal colic and concluded that both the drugs are equally effective and safe with added advantage of lornoxicam being more effective in early period[70].

In the present study total number of patients required paracetamol as rescue medication was n=14(17.5%). In group A (lornoxicam) n=3(7.5%) and in group B (diclofenac) n=11(27.5%)(Table 4). Patients required rescue analgesics following the first dose of the study drug in both the groups and the total rescue analgesic drug consumption was less in lornoxicam group when compared to diclofenac group. Similarly the utilisation of rescue drug was less with the drug lornoxicam in a study conducted by Sudip et al[1]. The difference

was highly significant ($p<0.019$, Table 4) showing better efficacy of lornoxicam when compared to diclofenac.

The time taken to use the first rescue medication in lornoxicam group was five hours and three hours in diclofenac group after the first dose of the study drug (Table 5), which showed the earlier utilisation of the rescue medication in diclofenac group. This is similar to study by Girija et al in which lornoxicam was compared with tramadol as postoperative management in patients undergoing elective gynecological surgery the results revealed that there was significant difference in time for rescue medication requirement between two groups . The time taken to utilise the first rescue analgesic was longer in lornoxicam (194.96±103.94 min) than the tramadol group (159.44±70.4 min) and the consumption of rescue analgesic was less in lornoxicam group (63.6±17.8) when compared to tramadol (64.2±21.86) group[71].

In the present study no patients dropped out from the study due to adverse effects. Totally 21 (26.25%) patients developed adverse effect in both the groups, 5(12.5%) patients in lornoxicam group and 16 (40%) patients in diclofenac group. Significantly more patients developed adverse reaction in diclofenac group ($p <0.005$, Table 6) which showed the better safety and tolerability of lornoxicam when compared to diclofenac.

The occurrence of nausea and epigastric pain (Table 7) was more in diclofenac group as compared to lornoxicam group. 7(17.5%) patients developed nausea and epigastric pain in diclofenac group and 2 patients developed nausea and no patients developed epigastric pain in lornoxicam group. This was supported by Nagendra S Chunduri et al in a study, efficacy of aceclofenac and diclofenac for relief of postoperative pain after third molar surgery which showed that nausea and epigastric pain were more in diclofenac group compared to aceclofenac group[66].

Dizziness and drowsiness were seen in 2 (5%) and 1(2.5%) patients respectively in lornoxicam group but no patients developed drowsiness and dizziness in diclofenac group. Dizziness seen in lornoxicam group could be one of the complications of mastoidectomy surgery[72]. Galani Varsha et al, also showed that lornoxicam had high tolerability and less gastrointestinal toxicity[7].In another comparative study in healthy volunteers lornoxicam 16mg/day showed significantly less gastrointestinal injury which was verified endoscopically when compared to naproxen 1000mg/day[45].

In the present study the Renal function parameters, blood urea and serum creatinine and liver function parameters like AST, ALT, alkaline phosphatase, total protein and total bilirubin did not show any significant variation after 72 hours as compared to baseline in both the groups. This was similar to study conducted by Turhan Togrul et[67]. In the present study the renal function parameters and liver function parameters were studied over a short

span of 72 hours, the nephrotoxicity and hepatotoxicity of these drugs cannot be commented in the present study.

However the difference between studies could be due to varying dosing schedule of lornoxicam and because of different types of surgical procedures. Lornoxicam, has been recently introduced in India and few number of placebo controlled and comparative clinical studies have shown that lornoxicam as an effective analgesic following surgery[45].

From the above results it was evident that lornoxicam (8mg twice daily) was found to be a better analgesic in terms of efficacy and tolerability when compared to diclofenac (75mg twice daily)in the management of postoperative pain following mastoidectomy surgery under local anesthesia .

The study population in both the groups showed satisfactory compliance. The limitations in our study were that, the subjects were not followed up after discontinuation of the drug for delayed adverse reaction. The present study was single blinded study with fairly small number of patients. So further studies with larger sample size, double blind design and long term follow up are necessary to investigate, further the effectiveness of drugs in relieving pain after mastoidectomy surgery.

CONCLUSION

Based on the results of our study we conclude that injection lornoxicam 8mg given intramuscularly is a better analgesic when compared to injection diclofenac 75 mg given intramuscularly in efficacy and tolerability in the management of postoperative pain following mastoidectomy surgery**.**

ABBREVIATIONS

IASP	-	International association for study of pain
ATP	-	Adenosine tri phosphate
TRP	-	Transient receptor potential
PTX3	-	Pentraraxin-3
GABA	-	Gamma aminobutyric acid
ORL	-	Opioid receptor like
TNF	-	Tumour necrosis factor
IL	-	Interleukin
AA	-	Arachidonic acid
PG	-	Prostaglandins
NOS	-	Nitric oxide synthase
NRS	-	Numeric rating scale
VAS	-	Visual analog scale
VRS	-	Verbal rating scale
FPS-R	-	Faces pain scale – Revised
WBS	-	Wong bakers pain rating scale
PAG	-	Periaqueductal grey

NSAID	-	Nonsteroidal anti-inflammatory drug
MOR	-	Mu opioid receptor
KOR	-	Kappa opioid receptor.
ALKP	-	Alkaline phosphatase
AST	-	Aspartate transaminase.
ALT	-	Alanine transaminase.
COX	-	Cycloxygenase
NAPQI	-	N-acetyl-p-benzoquinone imine
5HT	-	5 Hydroxy tryptamine
PCA	-	Patient controlled analgesia

APPENDIX – I

INFORMED CONSENT FORM

Study Title - **A Comparative study of Efficacy and Safety of Lornoxicam and Diclofenac as Postoperative Analgesics after Mastoidectomy Surgery**

Study Number _____

Subject's Full Name _____

Date of Birth/Age _____

Address _____

1. I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions. **OR** I have been explained the nature of the study by the Investigator and had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
3. I understand that the sponsor of the clinical trial/project, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.
4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)
5. I agree to take part in the above study

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative: _____

Signatory's Name _____ Date _____

Signature of the Investigator _____ Date _____

Study Investigator's Name _____

Signature of the Witness _____ Date _____

Name of the Witness

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
மருத்துவ ஆய்வில் பங்கேற்பதற்கு

ஆய்வு செய்யப்படும் தலைப்பு:

மேஸ்டாய்டு அறுவை சிகிச்சைக்கு பின் வலி நிவாரணம் குறித்து லார்னாக்சிகம் மற்றும் டைக்ளோபினாகின் பலன் மற்றும் பாதுகாப்பு குறித்து ஓர் ஒப்புயர்வு ஆய்வு.

பங்கு றெபவரின் பெயர் :

பங்கு பெறுபவரின் வயது :

		பங்கு பெறுபவர் இதனை குறிக்கவும்
1	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை நான் படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும் அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	☐
2	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
3	இந்த ஆய்வு சம்பந்தமாகவோ. இதைச் சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கையை பார்ப்பதற்கு என்னுடைய அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
4	இந்த அய்வின் மூலம் கிடைக்கும் தகவலையோ. முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
5	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் ஆய்வை மேற்கொள்ளும் மருத்து அணிக்கு உண்மையுடன் இருப்பேன் என உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ. அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.	☐

பங்கேற்பவரின் கையொப்பம் /..... இடம் ..... தேதி .....
கட்டை விரல் ரேகை
பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....
ஆய்வாளரின் கையொப்பம் /..... இடம் ..... தேதி .....
ஆய்வாளரின் பெயர் .....
மையம் .....
கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
சாட்சியின் கையொப்பம் /..... இடம் ..... தேதி .....
பெயர் மற்றும் விலாசம் .....

Appendix –I

லோர்னாச்சிகம் மருத்துவ ஆய்வில் பங்கேற்பதற்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்.

நான் _____ எனது மேஸ்டாய்டு எலும்பு அறுவை சிகிச்சைக்கு பிறகு வலி குறைப்பு மருந்து லோர்னாக்சிகம் கொடுத்தபின், பின் விளைவுகள் வர வாய்புகள் உள்ளது என மருத்துவர் மூலம் அறிந்து கொண்டேன். ஒவ்வாமை, வயிறுவலி, வாந்தி, சிறுநீரகம் மற்றும் கல்லீரல் பாதிப்பு ஏற்ப்பட வாய்ப்பு உள்ளது என்பதையும் அறிந்து கொண்டேன்.

அறுவை சிகிச்சைக்குப்பின் லோர்னாக்சிக்கத்தின் நன்மைகள் மற்றும் பின்விளைவுகள் அறிந்து சிகிச்சைக்கு முழு மனதுடன் சம்மதம் அளிக்கிறேன்.

கையொப்பம்,

APPENDIX – II

PROFORMA

GROUP:

Patient's Name: Date:

Age: Sex:

Weight:

Diagnosis:

Type of surgery: Duration of surgery:

History:

1. HT/DM/Asthma/seizure/bleeding diathesis
2. Liver /kidney disease / peptic ulcer
3. Hypersensitivity to drugs
4. Substance abuse/ Smoking
5. Drug intake – NSAID, sedatives, hypnotics, Psychotropic drug
6. Pregnancy / lactation
7. Previous surgery
8. Time of giving the test drug:
9. Name of the Drug given:

PAIN SCORE AND VITAL SIGNS

	1hr	3hr	6hr	12hr	24hr	48hr	72hr
VAS							
WBS							
PR							
RR							
BP							
Temp							

Adverse reaction :

Adverse events/ complaints (if any)

Hemodynamic parameters

	Hb%	TC	DC	ESR	BT	CT
Base line						
72 hrs after surgery						

Liver function test:

	Total protein	Total bilirubin	ALT	AST	ALK PHOS
Base line					
72 hrs after surgery					

Other parameters:

	Blood sugar	Serum creatinine	Blood urea
Base line			
72 hrs after surgery			

Usage of rescue medication: Yes/No

Time to use rescue medication:

Group A - Injection Lornoxicam 8 mg

S.No	Age	Sex	Group	Weigh t	SUR - Type	DUR - MIN	VAS _1	VAS_3	VAS_6	VAS_1 2	VAS_2 4	VAS_4 8	VAS_7 2	WBS_ 1	WBS_ 3	WBS_ 6	WBS_ 12	WBS_ 24	WBS_ 48	WBS_ 72	PR_1	PR_3	PR_6	PR_12	PR_24	PR_48	PR_72	SBP_1
1	24	2	A	60	1	90	2	2	3	3	2	0	0	2	2	2	2	2	0	0	80	76	70	70	74	74	70	110
2	27	2	A	58	1	90	2	2	3	3	2	1	1	2	2	4	2	2	0	0	80	74	78	70	74	70	74	110
3	40	2	A	68	1	90	1	3	2	1	1	1	0	2	2	2	2	2	0	0	76	74	74	74	74	74	74	114
4	23	2	A	62	1	90	2	3	1	3	3	2	2	2	2	2	2	2	0	0	80	74	74	76	80	80	80	114
5	19	1	A	64	1	90	4	3	4	4	2	2	2	4	4	4	4	2	2	2	80	80	84	80	74	74	78	118
6	18	1	A	59	1	90	4	4	3	3	3	2	2	4	4	4	4	4	2	2	74	74	70	78	78	80	80	110
7	33	2	A	65	1	90	3	3	2	2	2	1	0	4	4	2	2	2	2	0	70	70	78	78	70	80	80	112
8	21	1	A	72	2	120	2	2	3	4	2	1	0	2	2	2	4	2	2	0	72	70	74	76	70	70	76	112
9	25	1	A	68	2	90	2	2	2	2	3	1	0	2	2	2	2	2	0	0	74	74	74	78	78	78	80	110
10	19	2	A	56	1	60	2	2	2	2	3	1	0	2	2	2	2	2	0	0	80	76	80	80	84	84	80	110
11	22	1	A	70	2	90	2	2	2	2	3	1	0	2	2	2	2	2	2	0	80	80	76	76	80	80	80	110
12	29	2	A	59	2	90	1	3	1	1	2	2	0	2	4	2	2	2	2	0	80	80	76	74	74	80	74	114
13	47	2	A	72	1	90	2	1	1	1	3	3	1	2	2	2	2	2	2	0	80	80	76	76	76	80	80	114
14	20	1	A	60	1	90	2	1	1	1	0	0	0	2	2	2	2	0	0	0	80	80	80	80	74	74	74	110
15	25	1	A	64	1	90	4	2	2	2	1	0	0	4	2	2	2	2	0	0	80	80	76	76	78	78	78	114
16	29	2	A	59	1	90	1	3	1	1	2	2	0	2	4	2	2	2	2	0	70	70	72	80	78	78	74	110
17	47	2	A	72	2	90	2	1	1	2	2	2	0	2	2	2	2	2	2	0	74	70	70	70	70	78	74	110
18	19	2	A	58	2	120	4	2	2	1	2	1	0	4	2	2	2	2	2	0	70	78	80	80	74	70	70	120
19	20	1	A	65	1	90	3	2	2	1	2	1	1	4	2	2	2	2	2	2	80	80	74	76	80	80	80	110
20	34	1	A	68	1	90	2	2	2	3	3	2	2	2	2	2	4	4	2	2	80	80	76	76	76	76	76	110
21	26	2	A	60	1	90	4	2	2	2	4	2	1	4	2	2	2	4	2	2	80	84	80	77	80	80	74	110
22	42	2	A	65	1	90	3	2	2	2	2	2	1	4	2	2	2	2	2	0	76	74	72	80	78	78	74	112
23	28	2	A	65	1	75	2	2	2	3	2	2	2	2	2	2	4	2	2	0	74	74	74	70	70	72	70	112
24	35	1	A	68	1	75	2	2	3	3	2	2	2	2	2	4	4	2	2	2	70	70	72	70	74	74	70	114
25	19	1	A	70	2	90	2	2	0	1	2	0	0	2	2	0	2	2	0	0	82	70	74	74	74	72	70	110
26	28	1	A	72	1	90	2	2	2	1	1	1	0	2	2	2	2	2	2	0	84	70	74	74	80	82	80	110
27	29	2	A	66	2	90	2	2	2	2	2	1	0	2	2	2	2	2	2	0	80	70	70	72	74	70	70	100
28	21	2	A	58	1	90	2	0	1	2	2	2	0	2	0	2	2	2	2	0	70	72	70	74	74	70	70	100
29	37	2	A	69	1	75	2	0	0	1	2	2	0	2	0	0	2	2	2	0	72	74	70	74	70	70	72	110
30	22	1	A	64	1	90	2	1	0	0	1	0	0	2	2	0	0	2	0	0	70	72	74	74	72	70	72	110
31	49	2	A	70	1	90	3	2	2	1	1	1	1	4	2	2	2	2	2	2	72	74	74	74	72	70	74	110
32	47	2	A	65	2	90	2	2	2	0	0	0	0	2	2	2	0	0	0	0	70	72	74	74	72	70	72	112
33	23	1	A	68	1	75	3	1	1	1	1	1	0	4	2	2	2	2	2	0	70	70	72	74	70	72	74	110
34	27	1	A	63	1	90	2	1	1	1	1	0	0	2	2	2	2	2	0	0	70	74	72	74	70	72	70	112
35	34	1	A	72	2	90	4	2	2	2	0	0	0	4	2	2	2	0	0	0	70	74	72	72	70	74	70	110
36	27	1	A	60	1	90	3	2	2	1	1	0	0	4	2	2	2	2	0	0	74	72	70	72	70	70	72	112
37	46	2	A	68	1	75	2	2	1	1	1	0	0	2	2	2	2	2	0	0	74	72	70	72	70	70	70	110
38	38	2	A	74	1	90	2	1	1	1	1	1	0	2	2	2	2	2	2	0	74	74	70	70	70	74	72	120
39	36	1	A	73	1	75	4	2	1	1	1	0	0	4	2	2	2	2	0	0	74	70	72	70	74	70	76	110
40	34	1	A	72	2	90	2	1	1	1	1	1	1	2	2	2	2	2	2	0	74	70	72	76	78	70	78	110

Group A - Injection Lornoxicam 8 mg

SBP_3	SBP_6	SBP_12	SBP_24	SBP_48	SBP_72	DBP_1	DBP_3	DBP_6	DBP_12	DBP_24	DBP_48	DBP_72	HB_B	TC_B	DCN_B	DCL_B	DCE_B	ESR_B	PLA_B	BT_B	CT_B	DIRB_B	INDIRB_B	TOTB_B	ALT_B	AST_B	ALKP_B	TOTP_B
110	120	100	110	110	110	74	74	78	80	80	78	78	13.4	7,500	60	35	5	15	2.57	1.3	2.8	0.5	0.3	0.8	32	22	52	7
110	118	118	120	120	118	78	74	74	70	74	74	78	11.1	7100	50	45	5	14	2.23	1.2	2.3	0.4	0.3	0.7	32	24	50	7.2
110	110	110	120	118	120	74	78	78	70	70	74	72	13.8	9,100	55	45	5	12	3.3	2.55	3.3	0.4	0.3	0.7	30	25	49	7
118	120	120	118	120	120	80	82	82	78	80	80	82	12.5	8800	64	31	5	14	3.42	3.4	3.15	0.4	0.4	0.8	25	19	48	7.2
118	120	120	118	120	120	70	74	74	74	74	74	74	15.1	9800	63	34	3	14	3.66	1.4	2.2	0.3	0.3	0.6	26	25	49	7.5
110	114	120	110	112	110	70	74	74	70	70	70	70	14	7900	50	47	3	12	3.09	1.5	2.3	0.3	0.3	0.6	25	24	48	7.2
110	110	110	108	110	110	68	70	72	76	78	78	76	13.2	9700	58	39	3	15	2.38	1.3	3.3	0.3	0.3	0.6	27	22	52	7
110	108	110	114	110	110	68	72	70	70	74	74	70	15.3	7500	57	37	6	15	2.67	3	4	0.4	0.3	0.7	28	22	52	6.8
110	110	118	120	120	110	76	78	80	76	80	82	80	15.3	8900	58	40	2	15	2.79	2.3	3.5	0.2	0.5	0.7	27	21	50	7.3
110	108	108	110	110	108	70	76	76	72	70	70	70	12.8	9400	61	35	4	15	3.84	2.2	3.3	0.3	0.4	0.7	32	21	52	6.1
110	110	110	112	112	112	70	70	70	72	72	74	74	15.8	7300	55	42	3	14	2.12	2.23	4.35	0.5	0.2	0.7	26	20	51	6.4
110	112	110	112	110	110	76	70	72	74	74	70	70	13.3	6700	63	34	3	15	2.2	3.1	3.5	0.4	0.4	0.8	32	20	47	6.2
112	114	114	112	118	110	78	70	74	74	76	74	74	11.2	6200	57	40	3	14	3	2.5	3.45	0.4	0.4	0.8	32	22	48	6.8
110	114	112	112	112	114	78	80	78	78	80	80	80	13.2	7000	60	36	4	15	2.69	1.4	3.2	0.4	0.3	0.7	30	24	47	7.4
110	110	114	112	112	112	80	70	70	70	70	76	76	11.2	7700	55	40	5	12	2.68	1.35	2.5	0.5	0.3	0.8	32	24	48	6.5
110	110	116	114	110	110	70	80	70	74	80	74	74	15	9200	58	38	4	14	3.3	2.6	3.3	0.3	0.4	0.7	28	25	47	7.2
110	112	118	118	118	120	80	76	74	76	80	78	74	13.4	8400	65	31	4	14	2.54	1.36	4.2	0.4	0.4	0.8	26	20	52	6.2
118	120	118	118	120	120	84	74	72	74	76	80	74	15	6600	58	40	2	14	1.75	1.5	3.2	0.4	0.3	0.7	30	22	50	6.2
110	112	110	118	110	120	84	80	74	74	70	70	70	14.2	9600	74	23	3	13	3.79	2.5	4.2	0.4	0.4	0.8	28	24	50	7
118	118	120	120	114	120	80	80	78	70	74	74	74	15.5	7700	66	32	2	14	2.28	1.45	2.5	0.4	0.3	0.7	30	22	52	7.4
110	112	110	110	112	114	80	80	84	80	80	80	80	11.6	9300	60	35	5	15	1.97	1.4	2.5	0.4	0.2	0.6	32	21	50	7
114	112	112	112	114	120	78	78	80	80	84	80	80	11.5	5300	71	26	3	12	2.39	1.3	3.2	0.4	0.2	0.6	27	20	51	7.4
112	114	110	112	112	112	78	78	78	78	80	80	80	14.8	8400	70	28	2	12	2.65	2.4	3.2	0.2	0.4	0.6	26	25	50	6.8
114	116	116	116	114	110	78	78	78	80	80	84	80	13.2	7600	72	26	2	14	2.27	2.15	2.45	0.4	0.4	0.8	26	20	47	6.4
112	110	110	110	112	112	80	84	80	78	78	80	84	15.7	9500	60	35	5	14	2.17	1.25	2.45	0.3	0.4	0.7	32	25	47	6.2
110	110	114	110	110	110	82	80	80	80	80	78	78	14.1	7000	55	42	3	12	3.05	1.35	3	0.5	0.3	0.8	30	24	48	6.8
108	108	110	110	108	110	82	80	78	80	74	76	78	11.5	8500	68	30	2	14	2.93	2.15	4.45	0.3	0.5	0.8	30	24	48	6
110	110	108	110	110	110	82	80	74	80	74	78	80	11.8	6000	61	35	4	14	1.51	2	4.3	0.4	0.4	0.8	25	25	52	6.2
118	118	120	118	118	118	80	80	80	74	74	74	70	11.2	8000	70	28	2	15	4.09	1.35	2.4	0.4	0.3	0.7	32	25	48	6.2
112	110	108	110	110	110	80	84	84	84	82	80	80	13.4	9700	51	45	4	14	2.68	2.3	3.4	0.5	0.3	0.8	28	24	47	6.2
118	118	110	120	120	118	82	82	80	80	82	80	84	12.9	6400	58	37	5	14	3.11	2.2	3.4	0.3	0.4	0.7	30	25	48	7.1
110	110	110	112	114	112	84	84	84	86	80	80	80	13.8	9500	63	36	1	15	4.46	4	4.05	0.4	0.3	0.7	32	25	50	7.4
114	110	112	114	112	110	74	74	80	70	80	80	80	15	9800	66	32	2	12	2.45	2.2	3.3	0.4	0.3	0.7	25	20	50	7.3
114	110	112	114	114	110	80	82	78	70	70	70	70	15	6900	60	39	1	12	2.15	2.4	3.2	0.3	0.4	0.7	25	18	48	6.8
112	110	112	110	114	110	78	78	78	80	78	78	80	14.5	6100	53	44	3	14	2.48	1.2	3.35	0.4	0.3	0.7	30	20	47	7.4
114	112	114	110	110	112	80	80	80	82	78	76	76	15.5	9800	63	34	3	14	2.81	2.5	4.3	0.4	0.3	0.7	32	25	47	7.1
110	112	114	112	112	112	70	70	70	72	72	74	74	13.1	9900	54	45	1	12	3.18	2.3	3.2	0.4	0.2	0.6	30	24	50	7.1
118	110	110	112	110	110	70	74	70	70	70	70	74	11.2	9100	65	31	4	14	3.26	2.4	3.1	0.4	0.3	0.7	25	20	47	7.1
110	112	112	114	114	114	74	74	74	72	72	72	72	14.4	8200	65	32	3	14	2.65	3	4.45	0.4	0.3	0.7	26	22	51	7.2
110	112	110	110	112	112	74	74	72	72	74	74	74	14	7400	68	30	2	12	2.4	2.3	3	0.4	0.3	0.7	26	24	50	7.2

Group A - Injection Lornoxicam 8 mg

ALB_B	GLO_B	SUG_B	CRE_B	URE_B	HB_72	TC_72	DC N_72	DC L_72	DC E_72	ESR_72	PLA_72	BT_72	CT_72	DIRB_72	IND_72	TOTB_72	ALT_72	AST_72	ALKP_72	TP_72	ALB_72	GLOB_72	SUG_72	CRE_72	URE_72	RES DR	TIRE(HR	ADR
4	3	79	0.9	25	13.2	7800	66	30	4	15	2.8	1.2	3	0.3	0.4	0.7	27	22	49	7	4	3	80	0.9	25	2	0	1
4	3.2	103	0.8	26	11	7200	56	39	5	14	1.98	1.1	2.15	0.5	0.3	0.8	27	24	50	6.8	3.8	3	103	0.8	28	2	0	2
4	3.5	101	0.8	27	13.2	7500	59	36	5	12	2.56	2	3.1	0.4	0.3	0.7	31	22	48	7.1	4.1	3	90	0.8	26	2	0	1
4.2	3	96	0.8	25	12	8300	65	30	5	14	3.33	3.2	3	0.4	0.2	0.6	28	21	52	7.2	4.2	3	96	0.8	25	1	5	2
4	3.5	106	0.8	22	14.9	8800	67	32	1	12	3.64	1.4	2.2	0.4	0.3	0.7	27	20	49	7	4	3	84	0.7	26	2	0	2
4	3.2	81	0.8	28	14.2	7900	50	47	3	14	3.09	1.3	2.2	0.4	0.4	0.8	28	22	52	7.2	4	3.2	80	0.8	22	2	0	2
4	3	95	0.8	25	13.5	9100	58	38	4	14	2.35	1.5	3.4	0.4	0.4	0.8	31	22	52	6.2	3.2	3	98	0.9	28	1	7	2
4	2.8	92	0.7	27	15	6900	60	37	3	15	2.08	2.5	3.45	0.4	0.2	0.6	28	22	47	6.4	4.2	2.2	95	0.7	25	2	0	2
4.3	3	103	0.7	28	14.9	8400	58	40	2	14	2.25	2	2.8	0.3	0.4	0.7	27	21	52	7	4	3	86	0.7	23	2	0	2
4.2	1.9	86	0.8	22	12	9400	62	36	2	15	3.25	2.15	3.2	0.5	0.3	0.8	32	23	52	6.8	4.4	2.4	95	0.8	26	1	10	1
4.1	2.3	88	0.8	24	14.2	7000	56	42	2	14	1.89	2.2	4.35	0.4	0.3	0.7	28	22	48	6.4	4.4	2	88	0.8	26	2	0	2
3.8	2.4	102	0.7	26	12.8	6200	56	40	4	15	1.3	3	2.45	0.4	0.4	0.8	40	25	52	6.8	4	2.8	100	0.8	28	2	0	2
4.3	2.5	95	0.7	25	10.8	5800	56	42	2	15	2.36	2.55	3.5	0.4	0.3	0.7	30	20	49	6.9	4	2.9	100	0.7	28	2	0	2
4.6	2.8	85	0.7	27	12.8	6800	56	40	4	14	2.18	1.5	3.4	0.5	0.3	0.8	31	25	48	7	4	3	94	0.9	24	2	0	2
4	2.5	110	0.8	28	11.2	7400	63	36	1	14	2.14	1.3	2.5	0.7	0.4	0.7	31	28	52	7.2	4.2	3	102	0.9	28	2	0	1
4.2	3	90	0.7	25	14.5	8800	56	42	2	14	2.68	2.25	3	0.4	0.2	0.6	32	20	50	6.8	3.5	3.3	90	0.7	20	2	0	2
4	2.2	84	0.8	25	13	8000	64	32	4	14	2.05	1.3	4.25	0.4	0.3	0.7	28	18	52	6.8	4.1	2.7	80	0.8	26	2	0	2
4.1	2.1	81	0.7	21	15.8	6400	59	39	2	14	1.72	1.4	2.45	0.4	0.3	0.7	29	27	48	7	4.4	2.6	92	0.8	25	2	0	2
4	3	107	0.9	22	13.9	9400	70	25	5	14	3.24	2.45	4.1	0.3	0.5	0.8	27	18	52	6.4	3.2	3.2	95	0.8	25	2	0	2
4.4	3	110	0.8	26	15.5	7300	65	30	5	12	2.08	1.4	2.45	0.4	0.2	0.6	27	18	48	7	4	3	110	0.9	26	2	0	2
4.5	2.5	84	0.8	28	13.6	8100	68	30	2	13	2.2	2.45	3.4	0.4	0.4	0.8	28	22	48	7.2	4.6	2.6	95	0.8	28	2	0	2
4	3.4	112	0.8	26	12.8	7200	74	24	2	14	2.16	2	2.3	0.3	0.4	0.7	28	24	52	7.4	4.6	2.8	95	0.8	22	2	0	2
4.2	2.6	95	0.8	22	15.2	9800	60	36	4	13	2.14	2	2.3	0.4	0.3	0.8	32	24	48	6.4	3.8	2.6	104	0.8	26	2	0	1
4	2.4	84	0.6	24	13.8	6800	55	42	3	14	2.85	1.4	2.4	0.3	0.4	0.7	32	18	52	7	4.9	2.1	100	0.7	23	2	0	2
4.2	2	94	0.8	25	10.9	7400	73	26	1	14	2.42	2.3	4.2	0.4	0.4	0.8	27	18	48	6.4	4.9	1.5	95	0.8	22	2	0	2
4.5	1.3	94	0.8	23	11.2	5600	56	41	3	15	1.2	2.3	4.45	0.3	0.3	0.6	32	20	47	6.4	4.8	1.6	94	0.8	24	2	0	2
4.4	1.6	106	0.6	21	10.9	8500	73	26	1	15	2.93	2.15	4.2	0.3	0.4	0.7	30	20	48	6.4	4.9	1.5	100	0.6	22	2	0	2
4.4	1.8	82	0.7	27	11.2	5600	56	40	4	14	1.2	2.3	4.45	0.3	0.5	0.8	27	22	49	6.4	4.8	1.6	94	0.8	24	2	0	2
4.1	2.1	84	0.8	26	10.9	8400	72	29	1	16	3.85	2	2.5	0.3	0.4	0.7	28	23	52	6.4	4.3	2.1	90	0.8	26	2	0	2
4.2	2	95	0.8	25	12.9	9400	54	42	4	12	2.84	2.45	3	0.4	0.3	0.7	30	25	48	6.2	4.2	2	95	0.7	22	2	0	2
4.1	3	100	0.7	24	11.5	7000	57	38	5	14	2.58	2	3.2	0.3	0.4	0.7	31	20	50	7	4	3	95	0.6	28	2	0	2
4.2	3.2	102	0.8	27	13.2	9400	62	37	1	14	3.45	3.4	4	0.4	0.2	0.6	32	23	52	7.2	4.2	3	95	0.7	25	2	0	2
4.2	3.1	85	0.8	26	14.8	9400	64	34	2	12	2.45	2.2	3.3	0.5	0.2	0.7	30	27	50	6.5	3.3	3.2	85	0.7	25	2	0	2
4	2.8	78	0.6	22	14.5	6200	56	42	2	14	2.2	2.45	3	0.4	0.3	0.7	28	25	50	7	4.2	3.2	88	0.6	25	2	0	2
4.5	2.9	100	0.6	26	14.2	6000	58	39	3	12	2.52	2	3.2	0.4	0.3	0.7	28	25	52	7.1	4.1	3	95	0.9	22	2	0	2
4	3.1	94	0.8	22	14.8	9400	61	37	2	14	2.9	1.45	4.2	0.3	0.4	0.7	28	20	52	7	4	3	88	0.8	25	2	0	2
4.2	2.9	84	0.7	24	12.8	9600	54	45	1	14	2.54	2.2	3	0.4	0.3	0.7	27	28	50	7.2	4.2	3	94	0.8	28	2	0	2
4.1	3	94	0.8	28	11	9400	67	32	1	12	3.18	2.2	3	0.3	0.4	0.7	27	22	48	7.3	4.2	3.1	95	0.7	22	2	0	2
4.3	2.9	79	0.7	26	14.2	8600	62	34	4	12	2.42	2.4	3.3	0.2	0.4	0.6	28	28	48	7	4	3	85	0.8	25	2	0	2
4.2	3	98	0.9	25	14	7400	68	30	2	14	2.4	2.3	3.4	0.3	0.4	0.7	32	25	50	7.2	4.2	3	98	0.8	26	2	0	2

Group B - Injection Diclofenac 75 mg

S.No	Age	Sex	Group	Weigh t	SUR - Type	DUR - MIN	VAS _1	VAS_3	VAS_6	VAS_1 2	VAS_2 4	VAS_4 8	VAS_7 2	WBS_ 1	WBS_ 3	WBS_ 6	WBS_ 12	WBS_ 24	WBS_ 48	WBS_ 72	PR_1	PR_3	PR_6	PR_12	PR_24	PR_48	PR_72	SBP_1
1	18	1	B	65	1	90	8	4	2	3	5	3	3	8	4	2	2	6	4	4	94	100	80	80	90	80	80	110
2	22	2	B	58	1	90	10	8	4	4	7	6	1	10	8	4	4	6	6	2	96	110	90	90	100	90	80	100
3	27	1	B	65	2	120	8	8	8	6	4	4	2	8	8	8	6	4	4	2	100	110	110	90	94	84	84	120
4	18	2	B	56	1	90	5	5	8	6	3	2	2	6	4	8	6	4	2	2	100	90	100	84	84	80	80	110
5	21	1	B	60	1	90	5	5	5	4	3	3	2	6	6	6	4	4	4	2	94	94	90	84	84	76	78	110
6	19	2	B	62	1	90	5	5	6	6	4	2	2	6	6	6	6	4	2	2	90	90	90	84	90	84	90	110
7	35	2	B	60	1	90	6	5	8	7	6	6	5	6	6	8	8	6	6	4	100	96	100	90	90	80	80	100
8	34	2	B	70	1	60	5	5	4	5	4	4	2	6	6	6	6	4	4	2	80	80	76	80	80	82	82	110
9	19	2	B	60	1	90	5	5	6	4	4	4	3	6	6	6	4	4	4	2	80	80	84	80	80	84	80	110
10	27	2	B	64	1	90	6	5	4	4	4	4	3	6	6	6	4	4	4	2	80	80	80	84	84	80	76	110
11	35	1	B	68	1	90	5	5	4	8	2	3	2	6	6	4	8	2	4	2	80	80	84	86	86	86	80	110
12	31	1	B	72	1	90	5	5	5	5	5	4	2	6	6	6	6	6	4	2	80	84	82	82	82	80	76	110
13	33	1	B	75	1	90	5	4	4	4	3	3	2	6	4	4	4	4	4	4	80	84	84	80	82	80	80	110
14	27	2	B	58	1	75	7	6	5	4	4	4	4	8	6	6	4	4	4	4	80	84	84	80	80	84	84	110
15	19	1	B	62	2	90	5	5	5	8	5	4	3	6	6	6	8	6	4	4	80	86	84	80	80	84	82	110
16	35	2	B	62	2	120	4	4	4	5	4	4	2	4	4	4	6	4	4	2	80	80	84	84	86	80	80	110
17	35	2	B	63	1	90	7	5	5	4	4	3	2	8	6	6	4	4	4	2	80	84	84	80	80	84	80	110
18	25	2	B	62	1	90	5	4	4	4	4	4	2	6	4	4	4	4	4	2	80	84	84	86	80	86	84	110
19	22	2	B	59	2	120	5	5	5	4	4	2	2	6	6	6	4	4	2	2	80	84	86	84	84	84	84	110
20	45	2	B	60	1	90	6	6	5	5	4	4	2	6	6	6	6	4	4	2	80	84	84	86	84	84	80	110
21	25	1	B	76	2	90	6	5	5	5	5	4	2	6	6	6	6	4	4	2	86	84	80	74	76	74	80	112
22	35	2	B	62	1	90	5	4	4	5	4	4	3	6	4	4	6	4	4	4	80	84	80	84	82	80	80	110
23	30	2	B	68	2	120	6	5	4	3	3	4	2	6	6	4	4	4	4	2	80	80	80	78	80	84	84	120
24	40	2	B	62	1	90	5	5	4	4	4	4	3	6	4	4	4	4	4	3	80	80	84	84	82	82	82	110
25	32	2	B	64	1	90	6	6	6	6	5	4	2	6	6	6	6	6	4	2	84	84	84	82	80	82	80	112
26	33	1	B	75	1	90	5	6	5	5	5	4	4	6	6	6	6	6	4	4	80	80	84	82	84	80	80	112
27	34	1	B	68	1	90	6	5	5	5	5	5	4	6	6	6	6	6	6	4	70	74	80	80	78	80	80	110
28	20	1	B	62	1	90	5	4	6	6	5	5	4	6	4	6	6	6	6	4	80	80	84	82	84	84	84	110
29	32	1	B	68	1	90	5	4	7	6	5	5	5	6	4	8	6	6	6	4	80	84	84	84	84	86	86	110
30	25	1	B	62	1	90	6	6	6	6	5	5	4	6	6	6	6	6	6	4	80	84	84	84	82	84	84	110
31	19	2	B	54	2	90	6	7	6	5	4	4	2	6	8	6	6	4	4	2	80	84	80	84	84	84	80	112
32	45	2	B	68	1	75	4	5	6	6	5	5	4	4	6	6	6	6	6	4	86	88	88	88	88	86	80	110
33	29	2	B	56	1	90	5	4	4	6	5	4	4	6	4	4	6	6	4	4	80	78	78	78	78	80	80	110
34	37	1	B	70	2	120	5	5	6	8	6	4	4	6	6	6	8	6	4	4	80	80	84	78	78	78	76	118
35	33	2	B	58	1	75	5	5	4	4	4	4	3	6	6	4	4	4	4	4	78	78	80	80	80	84	80	120
36	19	1	B	64	2	90	4	4	3	3	2	2	0	4	4	4	4	2	2	0	80	80	80	84	84	80	76	110
37	19	1	B	68	1	75	5	5	7	5	4	4	2	6	6	8	6	4	4	2	80	84	84	80	80	76	76	112
38	35	1	B	75	1	75	6	6	5	4	4	2	0	6	6	6	4	4	2	0	80	76	70	74	72	70	70	114
39	25	1	B	75	1	90	6	6	5	5	5	4	2	6	6	6	6	6	4	2	84	76	76	74	70	78	70	110
40	23	1	B	65	2	90	7	6	8	6	6	4	4	6	6	8	6	6	4	4	80	72	74	72	74	80	80	110

Group B - Injection Diclofenac 75 mg

SBP_3	SBP_6	SBP_12	SBP_24	SBP_48	SBP_72	DBP_1	DBP_3	DBP_6	DBP_12	DBP_24	DBP_48	DBP_72	HB_B	TC_B	DCN_B	DCL_B	DCE_B	ESR_B	PLA_B	BT_B	CT_B	DIRB_B	INDIRB_B	TOTB_B	ALT_B	AST_B	ALKP_B	TOTP_B
110	120	120	120	120	120	70	70	70	74	74	70	70	13.7	10,500	59	26	15	14	2.37	1.58	3.28	0.6	0.5	1.1	32	18	52	7.2
110	110	110	110	120	120	60	60	70	70	70	70	70	12.3	5700	61	33	6	14	1.93	1.4	2.5	0.6	0.6	1.2	30	18	52	7
120	120	120	120	110	110	74	80	84	80	80	80	84	15.2	11,000	72	20	8	15	2.02	1.3	4.25	0.6	0.6	1.1	30	19	51	7.1
120	124	114	120	110	110	70	80	76	74	80	70	70	12.6	8000	62	32	5	14	2.18	1.3	4.2	0.5	0.5	1	32	19	50	7.1
110	120	120	124	120	120	80	80	80	74	74	70	70	15.4	10,500	71	24	5	12	3.1	1.1	2.3	0.5	0.5	1	30	20	52	7.4
110	110	120	112	112	110	70	70	80	70	70	70	70	13.7	7600	60	30	10	16	2.61	1.3	3.5	0.5	0.5	1	30	24	51	7.9
100	110	110	110	110	110	70	70	70	70	80	80	80	13.8	8,800	61	41	8	15	1.78	1	2.15	0.6	0.6	1.2	32	24	52	6.8
110	110	110	110	112	116	70	80	70	70	80	70	70	12.2	9400	60	31	9	16	3.17	2.3	2.5	0.5	0.4	0.9	31	21	52	6.9
110	114	114	110	110	114	70	70	80	80	70	70	70	13.5	8,100	53	41	6	18	2.24	2.2	2.3	0.4	0.6	1	30	21	49	7
110	112	112	110	116	110	70	74	74	70	70	76	76	11.6	9400	60	35	5	15	2.08	1.5	2.3	0.5	0.4	0.9	27	20	52	7.1
110	110	120	114	116	110	80	80	84	84	80	82	80	14.2	8,400	62	34	4	12	3.24	2.2	2.45	0.4	0.2	0.6	27	20	52	7
110	114	120	120	110	110	70	80	80	84	84	80	80	13.8	8200	62	36	2	16	2.45	2.2	3.15	0.3	0.3	0.6	27	20	50	6.8
110	112	120	120	110	120	70	80	84	84	82	80	80	16.4	7,600	52	46	2	15	2.43	1.3	2.5	0.4	0.4	0.8	28	21	50	6.6
110	114	114	120	110	116	70	70	80	80	80	70	74	12.7	7300	56	40	4	16	3.18	1.2	2.45	0.5	0.4	0.9	28	20	52	7.2
110	116	120	114	114	120	74	74	70	70	80	80	74	16	6,400	58	34	8	14	4.45	1.15	2.25	0.4	0.3	0.7	27	22	49	6.8
110	112	110	114	120	120	70	70	70	72	74	72	76	12.4	8600	60	32	8	15	3.4	2	3.4	0.4	0.2	0.6	27	22	50	7
110	110	112	112	110	110	70	70	74	74	74	74	70	12.8	9,400	64	34	2	14	2.68	2.15	3.3	0.2	0.3	0.5	28	22	48	7.1
110	118	116	120	118	118	70	70	74	80	70	70	74	13.7	8200	66	27	7	14	2.92	2.3	3.1	0.2	0.4	0.6	32	24	47	7.2
112	114	114	112	120	120	70	70	80	80	70	80	80	12.4	7,800	58	34	8	15	2.46	1.22	3.45	0.5	0.3	0.8	26	22	52	7.2
110	114	112	114	116	116	70	80	80	80	70	80	80	11.6	8000	52	40	8	16	2.93	2.2	3.4	0.3	0.4	0.7	28	25	52	6.8
112	114	112	120	120	120	76	76	76	74	74	74	80	14.6	8,700	60	31	9	14	4.3	1.15	3.2	0.2	0.3	0.5	26	26	51	6.7
110	114	112	116	118	118	80	78	82	78	78	74	80	12.6	7200	58	34	8	15	3.56	2.15	4	0.4	0.2	0.6	32	25	50	7.1
118	118	120	124	124	120	80	80	84	86	84	80	80	12.8	9,600	64	32	4	14	2.48	2.3	3.2	0.2	0.3	0.5	26	25	50	6.8
110	114	114	118	118	118	78	78	78	80	76	78	78	12.8	8400	64	30	6	16	2.64	2.4	3.2	0.4	0.4	0.8	32	25	52	6.6
110	110	110	112	118	118	72	70	70	74	76	76	76	12.2	8,400	56	40	3	16	3.45	2.15	2.1	0.3	0.5	0.8	26	24	52	7.2
110	112	114	118	118	120	74	74	74	74	70	70	72	15.4	7100	60	32	8	14	2.33	2.4	3.2	0.3	0.2	0.5	27	25	48	6.4
106	106	106	100	106	110	70	70	70	70	72	70	70	17.5	10,100	50	40	10	16	3.44	2.2	3.3	0.4	0.2	0.6	27	25	48	7
110	120	120	120	120	120	70	70	78	80	80	70	70	13.9	8900	65	30	5	15	3.45	2	3.2	0.4	0.1	0.5	26	24	49	7
110	110	120	120	120	110	70	70	76	76	80	80	80	13.8	7,800	67	28	5	12	3.23	2.15	3.2	0.4	0.2	0.6	28	25	50	7.3
110	110	120	120	120	110	70	80	70	70	80	80	70	12.2	6400	45	48	7	14	2.43	2.4	3.2	0.4	0.2	0.6	26	24	51	7.4
110	112	114	114	112	110	70	80	80	70	70	74	70	12.5	10,800	66	30	4	14	3.52	1.3	2.3	0.4	0.2	0.6	30	20	51	7
110	120	120	120	118	110	70	70	74	70	72	70	70	13.4	10200	60	34	6	12	4.19	2.4	3.2	0.4	0.2	0.6	26	25	52	7
110	110	110	118	116	116	70	70	70	74	72	72	70	13.1	10,400	65	30	5	14	3.33	1.1	2.35	0.2	0.2	0.4	27	22	50	7.2
118	120	116	116	110	110	70	72	72	74	74	74	70	13.8	9400	60	34	6	14	2.38	2.4	3.2	0.4	0.2	0.6	26	20	52	7
120	18	118	120	114	114	74	70	74	78	78	74	74	12.1	7,500	58	38	4	15	3.74	2.2	3.4	0.4	0.2	0.6	26	22	50	7.3
110	114	114	116	114	110	70	70	74	74	74	70	70	15.5	7300	56	40	4	15	2.91	1.55	3.22	0.3	0.2	0.5	28	20	50	7.2
112	114	114	114	120	114	70	74	74	70	70	70	70	14.9	8,800	60	38	2	14	3.01	1.1	2.5	0.4	0.3	0.7	30	22	52	6.7
114	114	110	110	112	110	74	70	72	74	70	70	70	13.2	7800	68	28	4	12	2.84	1.45	2.3	0.4	0.2	0.6	32	25	48	7
112	110	110	112	114	114	70	72	70	74	70	70	70	13.8	8,700	60	36	4	14	2.9	1.4	2.5	0.4	0.3	0.7	30	16	48	6.8
112	112	118	110	110	110	70	72	74	70	70	78	78	14	7200	57	40	3	14	3.75	2.3	3.5	0.5	0.3	0.8	32	25	50	7.2

Group B - Injection Diclofenac 75 mg

ALB_B	GLO_B	SUG_B	CRE_B	URE_B	HB_72	TC_72	DC N_72	DC L_72	DC E_72	ESR_7 2	PLA_7 2	BT_72	CT_72	DIRB_ 72	IND_7 2	TOTB_ 72	ALT_7 2	AST_7 2	ALKP_ 72	TP_72	ALB_7 2	GLOB_ 72	SUG_7 2	CRE_7 2	URE_7 2	RES DR	TI RE(HR	ADR
4.2	3	83	0.9	25	13.5	10300	64	25	11	14	2.42	1.52	3.28	0.2	0.5	0.7	27	18	50	7.4	4.3	3.1	80	0.8	26	2	0	2
4	3	93	0.6	20	12	6000	62	32	6	14	1.65	1.5	2.5	0.6	0.6	1.2	26	25	52	6.9	4	2.9	89	0.9	22	1	3	1
4.1	4	89	0.8	24	15	11000	68	24	8	15	2.01	1.3	4.2	0.6	0.5	1.1	32	24	50	6.9	4	2.9	80	0.6	24	1	6	1
4.1	3	89	0.9	22	11.8	7800	65	30	5	15	2	1.15	4.25	0.7	0.8	1.5	28	22	52	7.3	4.2	3.1	90	0.9	24	1	6	2
3.4	4	80	0.8	24	14.8	8100	68	27	5	16	2.86	1.1	2.3	0.4	0.4	0.8	30	21	47	7.2	3	4.2	90	0.8	25	2	0	1
3.5	4.4	92	0.8	26	13.2	7800	58	35	7	12	2.23	1	3	0.5	0.5	1	30	20	52	7.2	2.8	4.4	92	0.8	26	2	0	1
3.4	3.4	105	0.8	20	13.2	8700	52	42	6	16	1.65	1.15	1.3	0.7	0.8	1.5	28	18	48	6.9	3.3	3.6	90	0.7	22	1	6	2
4	2.9	100	0.9	22	11.8	8600	63	24	13	16	2.8	2	2.2	0.6	0.6	1.2	31	18	48	6.8	4	2.8	100	0.9	24	2	0	1
4	3	90	0.6	21	13.3	7300	55	40	5	14	2.18	2.18	2.35	0.5	0.7	1.2	32	19	50	6.8	4.2	2.6	90	0.6	21	2	0	2
4.1	3	94	0.8	25	11.2	9300	61	34	5	15	1.98	2.3	2.45	0.4	0.4	0.8	27	22	49	6.9	4.2	2.6	104	0.9	25	2	0	2
4.2	2.8	90	0.9	24	13.8	8000	64	32	4	14	3.08	2.1	2	0.4	0.3	0.7	27	21	49	6.8	4.2	2.6	95	0.8	22	1	12	2
4.2	2.6	90	0.6	24	13.8	8200	62	36	2	16	2.25	2.15	3.3	0.4	0.3	0.7	28	24	52	6.6	4	2.6	95	0.8	25	2	0	2
4.2	2.4	106	0.9	25	16.4	8000	52	46	2	15	2.68	1.45	2.4	0.3	0.4	0.7	30	24	52	7	4.2	2.8	94	0.8	24	2	0	1
4.2	3	88	0.9	25	11.8	7400	56	40	4	14	2.64	2	3.2	0.4	0.3	0.7	28	25	50	6.9	4	2.9	88	0.8	24	2	0	1
4.4	2.4	106	0.8	28	14.8	7200	56	38	6	16	3.86	2	2.4	0.5	0.3	0.8	28	24	48	6.8	4.2	2.6	101	0.8	26	1	12	2
4.2	2.8	105	0.7	24	12.2	8400	62	30	8	15	2.84	2.2	3.45	0.4	0.3	0.7	27	20	47	7.1	4.3	2.8	95	0.6	26	2	0	2
4.3	2.8	95	0.6	24	12.4	9600	66	32	2	15	2.68	2.15	3.3	0.3	0.3	0.6	27	18	47	7	4.2	2.8	90	0.7	26	2	0	1
4.6	3.2	84	0.8	26	13.8	9000	70	23	7	15	2.92	2.54	3.4	0.3	0.3	0.6	28	22	71	7.2	4.1	3.1	95	0.9	26	2	0	1
4.2	3	90	0.7	27	12.1	8000	48	44	8	15	2.46	1.22	3.45	0.3	0.2	0.5	27	18	48	7	4	3	88	0.8	27	2	0	2
4	2.8	107	0.8	24	11.2	8000	52	40	8	14	2.93	2.2	3.4	0.4	0.2	0.6	28	24	50	7	4	3	96	0.9	25	2	0	1
4.2	2.5	101	0.6	26	14.3	8400	61	34	5	14	3.8	1.2	3.4	0.2	0.2	0.4	28	18	48	7	4	3	109	0.8	25	2	0	1
4.2	2.9	108	0.8	26	12.6	7200	48	44	8	14	3.56	2.15	4	0.4	0.2	0.6	24	25	47	7.1	4.2	2.9	95	0.6	25	2	0	2
4.2	2.6	105	0.9	25	12.7	9900	64	32	4	16	2.59	2.15	3.4	0.2	0.3	0.5	28	19	50	7	4.3	2.7	94	0.8	28	2	0	2
4	2.6	94	0.9	20	12.2	8600	68	27	5	16	2.16	2.15	3	0.4	0.4	0.8	28	25	47	7	4.2	2.8	102	0.8	26	2	0	2
4.1	3.1	90	0.7	26	12.2	8400	56	40	4	16	2.86	2.1	3.4	0.4	0.3	0.7	25	20	48	7	4	3	96	0.8	25	2	0	2
4.2	2.2	86	0.9	26	13.7	6400	60	31	9	15	2.04	2.2	3.4	0.5	0.5	1	27	24	50	6.8	4.4	2.4	82	0.9	22	2	0	1
4.5	2.5	81	0.9	28	17.1	9300	51	44	5	14	2.93	2.4	3.15	0.5	1	1.5	30	20	51	7.2	4.6	2.6	82	0.8	24	2	0	1
4.1	2.9	95	0.5	25	13.9	8750	64	31	5	15	3.42	2.15	3.4	0.4	0.2	0.6	29	24	50	6.9	4	2.9	86	0.6	26	2	0	2
4.2	3.1	108	0.6	26	13.8	7800	70	25	5	14	3.1	2.2	3.4	0.3	0.2	0.5	25	25	52	7.2	4.1	3.1	102	0.8	25	1	6	2
4.2	3.2	77	0.8	27	11.8	6800	53	42	5	15	2.56	2.2	3.4	0.4	0.1	0.5	30	18	47	7.1	4.1	3	90	0.6	25	2	0	2
4	3	91	0.7	27	11.8	10,500	65	31	4	14	2.54	2	2.4	0.3	0.2	0.5	32	20	52	7.2	4.2	3	94	0.6	22	1	3	1
4.2	2.8	89	0.9	23	12.8	9600	54	40	6	15	3.45	2.2	3	0.4	0.3	0.7	36	22	48	7.4	4.3	3.1	82	0.7	24	2	0	2
4.1	3.1	80	0.8	22	12.8	9800	68	27	5	15	2.56	2	2.4	0.3	0.2	0.5	32	19	50	7.1	4.1	3	85	0.9	22	2	0	2
4.5	2.5	90	0.8	22	13.4	9400	60	35	5	14	2.32	2.3	3.4	0.4	0.3	0.7	28	25	59	7.1	4.5	2.6	95	0.9	25	1	12	2
4.1	3.2	99	0.8	24	11.8	7600	60	38	2	15	3.54	2.4	3	0.3	0.2	0.5	30	25	49	7.4	4.3	3.1	95	0.9	26	2	0	2
4.2	3	85	0.8	27	14.8	7200	57	37	6	15	2.45	2	3.15	0.2	0.2	0.4	26	20	52	7.2	4.2	3	90	0.7	26	2	0	2
4	2.7	78	0.7	27	14.8	8400	62	36	2	14	2.8	1.45	2.5	0.4	0.2	0.6	30	22	48	6.8	4.1	2.7	85	0.8	28	1	6	1
4	3	85	0.8	25	13	7800	69	27	4	12	2.75	1.45	2.3	0.4	0.3	0.7	30	19	47	7.2	4.2	3	80	0.9	26	2	0	2
4.1	2.7	80	0.8	26	14.2	8600	60	38	2	14	2.75	2	2.4	0.5	0.3	0.8	28	22	49	7.4	4.2	3.2	90	0.8	25	2	0	2
4.2	3	85	0.8	22	14	7000	58	38	4	12	2.2	2.2	3.5	0.5	0.4	0.9	26	20	50	7.2	4	3.2	100	0.9	22	1	6	1

BIBLIOGRAPHY

1. Sudip kr.Das, Manasi Baneerjee, shirsendu Mondal, Balaram Ghosh. A comparative study of efficacy and safety of Lornoxicam versus Tramadol as analgesics after surgery on head and neck . Indian Journal of Otolaryngology Head Neck Surgery 65(1) (2013) 126-S130.

2. Angela Banks, RN, Innovations in Postoperative Pain Management: Continuous Infusion of Local Anesthetics AORN Journal, 2007, 85 (5)904-918

3.Turhan Togrul ,Zeynep Baysal Yildirim , Mustafa CENGIZ,Imran San . Comparison of intravenous paracetamol and tramadol for postoperative analgesia in patients with Septo Rhinoplasty ,Journal of Anasthesia 19(4) (2011)213-216.

4.Teena Bansal ,Anil Takur,SaralaHooda. Comparison of efficacy of lornoxicam and diclofenac for postoperative pain relief in patients undergoing abdominal hysterectomy, International Journal of Pharmacy and Pharmaceutical sciences 3 (4) (2011)

5.Bahadir Daglar ,Hasan Kogoglu ,M.Adnan Celkan ,Sitki Goksu ,Hakki Kazaz.Comparison of the effectsof Lornoxicam versus Diclofenac in pain management after cardiac surgery : A single-Blind Randomized Active-Controlled study, Curr Therap 66 (2005) 107-16

6.Mohamed Daabiss, Medhat Al-Otaibi and Rima Al-Nimar. Analgesia in day–case ENT surgery : the efficacy of Lornoxicam, British Journal Medical Practitioners. 2 (3) (2009) 46-50.

7.Galani Varsha J ,Patel Nimesh A, Bhart R Dave ,Ajay Krishnan ,A comparison of the efficacy and tolerability of Lornoxicam and Diclofenac sodium in patients with acute postoperative pain after Spinal Surgery, American Journal Of Phytomedicine and Clinical Therapeutics (2013) 507-515.

8. Satish deshpande, Principles of anesthesia, 2007, Paras medical publisher, 845-847.

9. Ronald D Miller, Miller's Anasthesia, 6th edition,2005, Elsevier, 2729-2737.

10. Kenneth F Swaiman, Stephen Ashwal, Donna M Ferriero, Pediatric Neurology Principles and practice, volume 2, 4th edition, 2006, Elsevier, 2373-2379.

11.Kim E Barret, susan M Barman Scott Bortan Heddwen L.Brooks, Ganong's Review of Medical Physiology, 23rd edition ,2010, Lange ,167-170.

12.John E Hall, Arthur C Guyton, Text book of medical physiology, 12th edition, 2011, Elsevier, 583-587.

13. Allen H Robert H Brown, Adams and victor's principles of neurology, 8th edition, 2005, Mc Graw Hill, 111-116.

14.Walter G Bradley , Robert B Daroff, Gerald M Fenichel, Joseph Jankovic, neurology in clinical practice, 5th edition, volume-1, 2008, Elsevier, 899-901.

15. Edward R. Perl, Pain Mechanisms, A Commentary on Concepts and Issues, NIH Public Access Author Manuscript, PMC 2012 June 1, 1-41.

16.Massieh Moayedi and Karen D Davis, Theories of pain: from specificity to gate control, Journal Of Neurophysiology, oct 3, 2012, 5-12.

17. Daniel MOTOC, Nicoleta clarisa TURTOI, Virgil VASCA, Elisabeta VASCA, Francis C SCHNEIDER, Physiology of pain – general mechanism and individual differences , journal of Aradean , vol13, (4) , 2010, 19-23.

18. Clinical aspects of Acute Post-operative Pain management & Its assessment, J Adv Pharm Technol Res, 2010, Apr-Jun; 1(2), 97–108.

19.Longo Fauci, Kasper Hauser Jameson Loscalzo, Harrison's principles of Internal Medicine , 18th edition, volume-1, 2012, McGraw Hill, 93-96.

20. Eric R Kandel ,James H Schwartz ,Thomas M Jessell, Steven A Siegel baum, AJ .Hudspeth, Principles of neural science, 5th edition ,530-555.

21. Bruce M Koeppen, Bruce A Stanon, Berny and Levy Physiology 6thedition, 2009, Elsevier, 114-116.

22. H.P.Rang, M.M. Dale, J.M. Ritter, R.S.Flower, G.Henderson, Rang and Dale's Pharmacology, 7th edition, 2012,Elsevier, 503-511.

23.Cedric Prys Roberts, Burnell R Brown , International Practice of Anaesthesia, Volume -1,Butterworth Heinemann , International edition, 1-21.

24. Lawerence Brunton Bruce Chabner Bjorn Knollman , Goodman and Gilman's The pharmacological basis of Therapeutics , 12th edition, 2011, McGraw Hill, 486-490.

25. Ream Al –Hasani, Michael R Bruchas, Molecular mechanisms of opoid receptors – Dependent signaling, and behavior, Anesthesiology NIHPA Author manuscript PMC 2013, July 2, 1-9.

26.Vinay kumar, Abdul K Abbas, Nelson Fausto, Robbin's and Cotran Pathologic basis of diseases 7th edition, 2004, Elsevier, 48-50.

27. Raphael Rubin, David S Strayer, Rubin's pathology Clinicopathologic foundations of medicine ,6th edition, 2012, Lippincott William & Wilkins,47-66.

28. John M Kissane, Anderson's Pathology volume 1, 9th edition, 1990, international edition, 22-43.

29. Harshmohan, Text Book of Pathology, 4th edition, 2000, Jaypee, 114-131

30. Vinay kumar, Abdul K Abbas, Nelson Fausto, Robbin's and Cotran Pathologic basis of diseases 7th edition, 2004, Elsevier, 63-75.

31. G.Edward Morgan, Maged S, Mikhail J Murray, Clinical Anasthesiology, 4th edition, 2006, McGraw Hill, 471-472.

32.Elsa Wuhrman, Maureen F Cooney, Acute Pain: Assessment and treatment, www.medscape.com, 1-14

33.George Shorten, Daniel Carr, Postoperative Pain Management an Evidence Based guide to practice, 2006, Elsevier, 102-108.

34. Agnes Paul Dauphin, Francis Guillemin, Jean-Marc virion and Serge Briancon, Bias and precision in Visual Analogue Scales: A Randomized Controlled Trial, American Journal of Epidemiology, vol 150(10), 1999, 1117-1127.

35. Deborah Tomlinson, Carl L Von Baeyer, Jennifer N Stinson and Lillian Sung, A Systematic Review of Faces Scales for the Self-report of Pain Intensity in Children, Journal of the American Academy of Pediatrics,oct4, 2010,1168-1174

36.Gillian A.Hawker, Samra Mian, Tetyana Kendzerska and Melissa French, Measures of Adult Pain, American College of Rhematology, vol63(11), November 2011, 240-252.

37.Gregory Garra, Adam J Singer, Breena R Taira ,Jasmin Chohan, Hiran Cardoz, Ernest Chisena and Hendry C Thode, Validation of the Wong-Baker FACES Pain Rating Scale in Pediatric Emergency Department Patients, ACAD EMERG MED , Jan 2010, vol 7 (1),50-54.

38. Charles E. Argoff, Recent Management Advances in Acute Postoperative Pain, World Institute of Pain, Pain Practice, 2013,1-11.

39. Lawerence Brunton Bruce Chabner Bjorn Knollman , Goodman and Gilman's The pharmacological basis of Therapeutics , 12th edition, 2011, McGraw Hill, 497-521.

40.Hanna Misiołek, Maciej Cettler, Jarosław Woroń, Jerzy Wordliczek, Jan Dobrogowski, Ewa Mayzner-Zawadzka, The 2014 guidelines for post-operative pain management, Anaesthesiology Intensive Therapy, 2014, vol. 46(4), 221–244.

41.Bertam G Katzung Anthony J Trevor, Basic and Clinical Pharmacology 13th edition, 2015, McGrawHill, 544.

42. Ream Al-Hasani and Michael R. Bruchas, Molecular Mechanisms of Opioid Receptor-Dependent Signaling and Behavior, Anesthesiology, NIH Public Access Author manuscript, December 2011, 115(6), 1363–1381.

43. Lawerence Brunton Bruce Chabner Bjorn Knollman , Goodman and Gilman's The pharmacological basis of Therapeutics, 12th edition, 2011, McGraw Hill,982-992.

44. G.Edward Morgan, Maged S, Mikhail J Murray, Clinical Anasthesiology, 4th edition, 2006, McGraw Hill, 498-499.

45. Godara Sushila, Srivastava R K, Godara Rajesh, Bhutani Garima, Lornoxicam: a review of its therapeutic potential in different clinical studies, Journal of Drug Delivery & Therapeutics; 2013, 3(2), 145-148

46. Bertam G Katzung Anthony J Trevor, Basic and Clinical Pharmacology 13th edition, 2015, McGrawHill, 621-621.

47. George Shorten, Daniel Carr, Postoperative Pain Management an Evidence Based guide to practice, 2006, Elsevier,

48. G. Edward Morgan, Maged S, Mikhail J Murray, Clinical Anasthesiology, 4th edition, 2006, McGraw Hill, 334-335

49. Derald E Brackmann, clough Shelton, Moises A.Arriaga, Otologic surgery, 3rd edition, 2010, Saunders Elsevier, 195-207

50. K.K.Ramalingam,B.Sreeramamoorthy, RaviRamalingam, A Short practice of otorhinolaryngology, 4th edition, 2014, All India publishers and distributors, 414-415.

51. Derald E Brackmann, clough Shelton, Moises A.Arriaga, Otologic surgery, 3rd edition, 2010, Saunders Elsevier, 173-181.

52. Michael E Glasscock, Aina Julianna Gulya, Shambaugh, Surgery of the Ear, 5th edition, 2003, B C Decker Inc, 786-791.

53. Newton J Coker, Herman A Jenkins, Atlas of otologic surgery, 2001, W.B. Saunders company, 239-249.

54. P L Dhingra , Diseases of Ear, Nose and Throat, 5th edition, 2010, Elsevier, 409-415.

55. Gul caner, Levent olgon, Gurol Gultekin, Levent Aydar, Local Anasthesia for Middle Ear Surgery, Otolaryngology Head and Neck surgery, 133, 2005, 295-297.

56. Charles W.Cummings, Paul W Flint, Lee A Harker, Bruce H Haughey, Mark A Richardson, K.Thomas Robbins, David E Schuller, J.Regan Thomas, Otolaryngology Head and Neck Surgery, 4th edition, volume 4, 2005, Elsevier, 3075-3086.

57.Prasad Byrav D S, B Medhi, A Prakash, S Patyar, S Wadhwa, Lornoxicam: a Newer NSAID, IJPMR 2009; 20 (1),27-31

58.Yifan Zhang, Dafang Zhong, Dayong Si, Yingjie Guo, Xiaoyan Chen & Hui Zhou, Lornoxicam pharmacokinetics in relation to cytochromeP450 2C9 genotype, British Journal of Clinical Pharmacology, 2005, vol59(1), 14-17

59.Vishalkumar K. Vadgama, Ripal Gharia, Kalpesh Mehta, Ravisaheb Sanjiv and C B Tripathi, A Randomized Controlled Clinical Trial Comparing Efficacy, Safety and Cost Effectiveness of Lornoxicam with Diclofenac Sodium in Patients of Osteoarthritis Knee, Internet Journal of Medical Update 2011, 6(2), 25-29.

60. Sener M, Yilmazer C, Yilmaz I, Bozdogan N, Ozer C, Donmez A, Efficacy of lornoxicam for acute postoperative pain relief after septoplasty: a comparison with diclofenac, ketoprofen and dipyrone. Journal of Clinical Anesth 2008, 20,103-108.

61. Sapolya O, Karamanhoglu B, Memis D,Analgesic effects of lornoxicam in postoperative analgesia after total abdominal hysterectomy, Journal of Opioid Manag , 3, 2007, 155-159.

62. Anirban Pal, Jhuma Biswas, Purnava Mukhopadhyay, Poushali Sanyal, Shyamal Dasgupta, Shyamashis Das, Diclofenac is more effective for post‑operative analgesia in patients undergoing lower abdominal gynecological surgeries: A comparative study, Anesthesia: Essays and Researches, 8(2), 2014, 192-196.

63. Ashima Taneja, Vidhushi, Tanudeep Kaur, Indu Veena Sood, Comparative Study on The Effect of Paracetamol, Diclofenac and their Combination in Post Operative Pain Relief of Cesarean Section, JK science, 17(1), 2015, 30-32.

64. Cengiz Kara, Berkan Resorlu, Izzet Cicekbilek, Ali Unsal, Analgesic Efficacy and Safety of Nonsteroidal anti-inflammatory drugs after Transurethral resection of prostate, Int Braz J Urol, 36 (1), 2010, 49-54.

65. Ashraf A Abdelhalim, Sami Al harethy, Mohamed Moustafa, Lornoxicam versus tramadol for post-operative pain relief in patients undergoing ENT procedures, Saudi Journal of Anasthesia , 8(1), 2014, 38-44

66. Nagendra Srinivas Chunduri, Efficacy of aceclofenac and diclofenac sodium for relief of postoperative pain after third molar surgery: A randomised open label comparative study, Journal of Pharmacology and Pharmacotherapeutics , 4(2) 2013, 144-145

67.Turhan Togrul, Zeynep Baysal Yildirim, Mustafa Cengiz, Ali Cigdem, Comparison of intravenous paracetamol and tramadol for postoperative analgesia in patients with septo-rhinoplasty, 19(4), 2011, 213-216

68.Geetha Bhandari, Kedar Singh Shahi, Rajni Bhakuni, Anesthesia, Essays And Researches Medknow Publications, 7(2), 2013, 243-247.

69. Dae Wook Lee Hyung Gon Lee and Seong Heon Lee, Postoperative Nausea And Vomiting After Mastoidectomy With Tympanoplasty: A Comparison Between TIVA With Propofol-Remifentanil And Balanced

Anesthesia With Sevoflurane-Remifentanil, Korean Journal Of Anesthesiology, 2011. 61(5), 399-404.

70. Sushila Godaraa, R. K. Srivastavaa, M. G. Vashistb, Rajesh Godarab, Lornoxicam versus diclofenac sodium in acute renal colic: a prospective randomized trial, International Journal of Basic & Clinical Pharmacology, March-April 2013, Vol 2 (2),193-198

71. Girija. B. S, Sahana G. N, Chandrakumar, Sudha T. R, Comparison of efficacy and tolerability of Tramadol with Lornoxicam as postoperative pain management by administering pre-emptively in patients undergoing elective gynecological surgery under regional subarachnoid block anesthesia, International Journal of Biological & Medical Research, 4(2), 2013, 3037-3040.

72. Mastoidectomy University of Maryland Medical Centre

http://umm.edu/health/medical/ency/articles/mastoidectomy#ixzz3lDwWIsCL